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PELLAGRA

PART I.

A New Contribution to the Etiology and Pathogenesis
of Pellagra.
Preliminary Note of May 25th, 1913.

A New Contribution to the Etiology and Pathogenesis
of Pellagra,
Monograph of 1914.

By Professors (Giulio Alessandrini) and Alberto Scala of the
Institute of Experimental Hygiene of the
University of Rome.

Illustrated with the Original Plates, and Drawings
made by the translator.

Translated from the Italian
by E. M. Perdue, A. M., M. D., D. P. H.

PART II.

PELLAGRA IN THE UNITED STATES

By E. M. Perdue, A. M., M. D., D. P. H., Prof. of Preventive
and Tropical Medicine, Eclectic Medical University,
Director Johnson's Pathological Laboratory for
Cancer Research, Kansas City, Mo.,
President American Association
of Progressive Medicine.

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E. M. PERDUE,
KANSAS CITY, MO.

DEDICATION.

To my friends, Giulio Alessandrini and Alberto Scala, of the Institute of Experimental Hygiene of the University of Rome, in recognition of their epoch making achievements in the field of scientific medicine, this volume is respectfully inscribed.

PREFACE.

Medical research in the United States is involved in unscientific chaos for the following reasons:

1. It is founded upon hypotheses instead of upon facts.
2. In animal experimentation it ignores the Postulates of Koch.
3. It discredits clinical findings.
4. It refuses to acknowledge the clinically obvious.
5. It is committed to therapeutic nihilism.
6. It ignores scientific truth not conforming to its hypotheses.
7. It ignores other lines of scientific endeavor.
8. It refuses scientific research not originating in Germany.
9. It is committed to the tedious, abstruse, impossible German method.

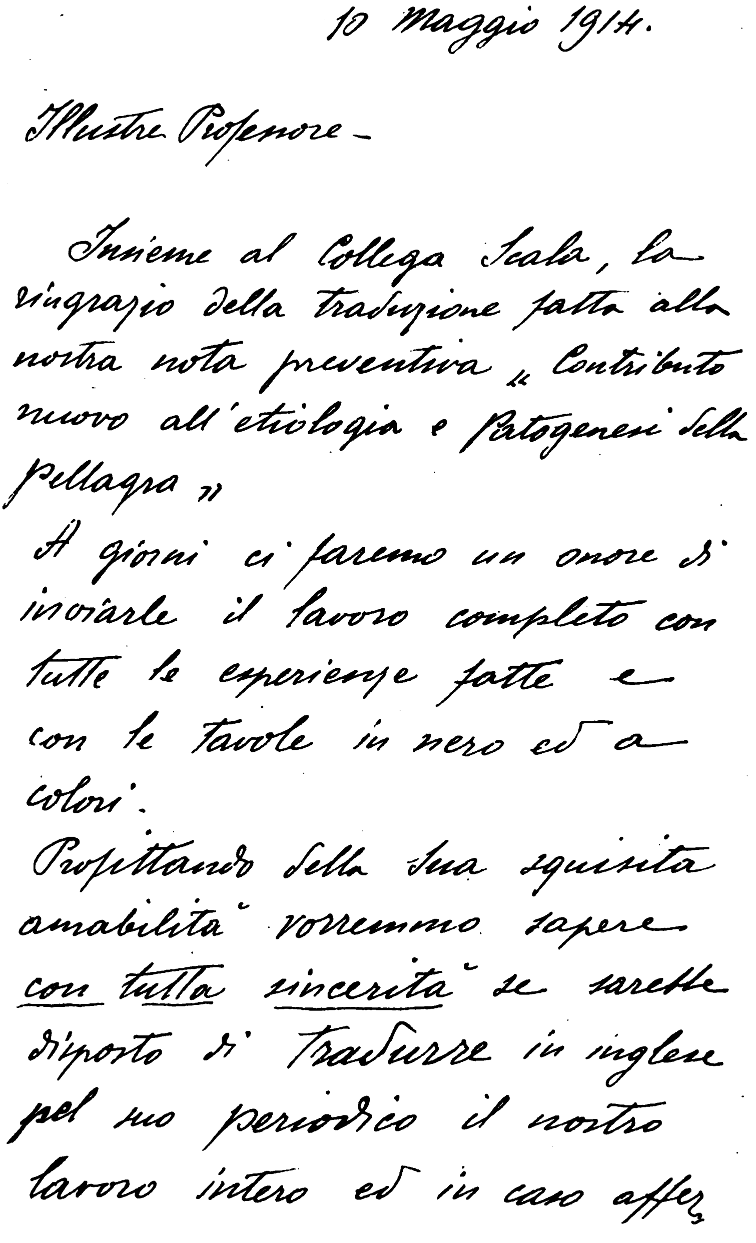
The above conditions apply to research in pellagra in the United States. In this work it is a pleasure to present the modern scientific method and the determination of the cause, prevention and cure of pellagra.

Professors Alessandrini and Scala of the Institute of Experimental Hygiene of the University of Rome published their Preliminary Note in May, 1913. They sent the writer a copy. He translated it into English and sent them copies. They sent their complete monograph and requested its translation and publication in English. For this purpose they sent the original cuts with which their work was illustrated.

We have duplicated their research in our laboratories here. In the second part of this work we have applied their conclusions to the geographical distribution of pellagra and clay soils in the United States.

To Professors Alessandrini and Scala is due the honor and credit of a discovery and demonstration second to none in the progress of scientific medicine in the last twenty years. It is a pleasure to be able in any measure to second their efforts and to give their work to an English speaking profession.

E. M. P.



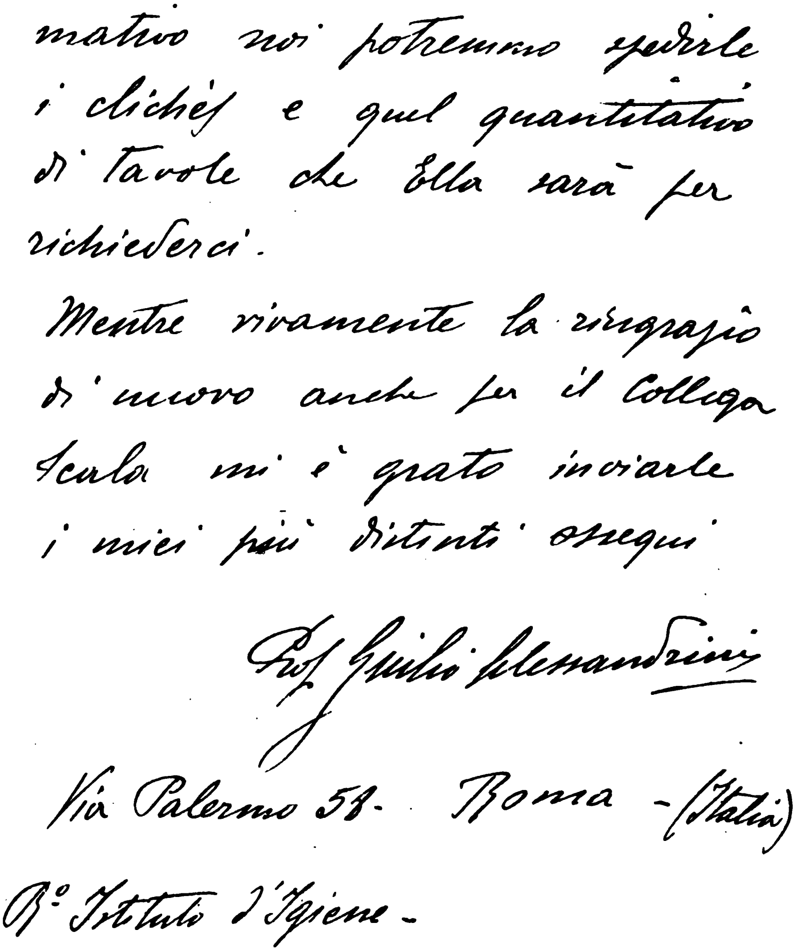
10 maggio 1914.

Illustre Professore -

Insieme al Collega Scala, la ringrazio della traduzione fatta alla nostra nota preventiva „ Contributo nuovo all'etiologia e patogenesi della pellagra "

A giorni ci faremo un onore di inviarle il lavoro completo con tutte le esperienze fatte e con le tavole in nero ed a colori.

Profittando della sua squisita amabilità vorremmo sapere *con tutta sincerità* se sarebbe disposto di tradurre in inglese pel suo periodico il nostro lavoro intero ed in caso affer-

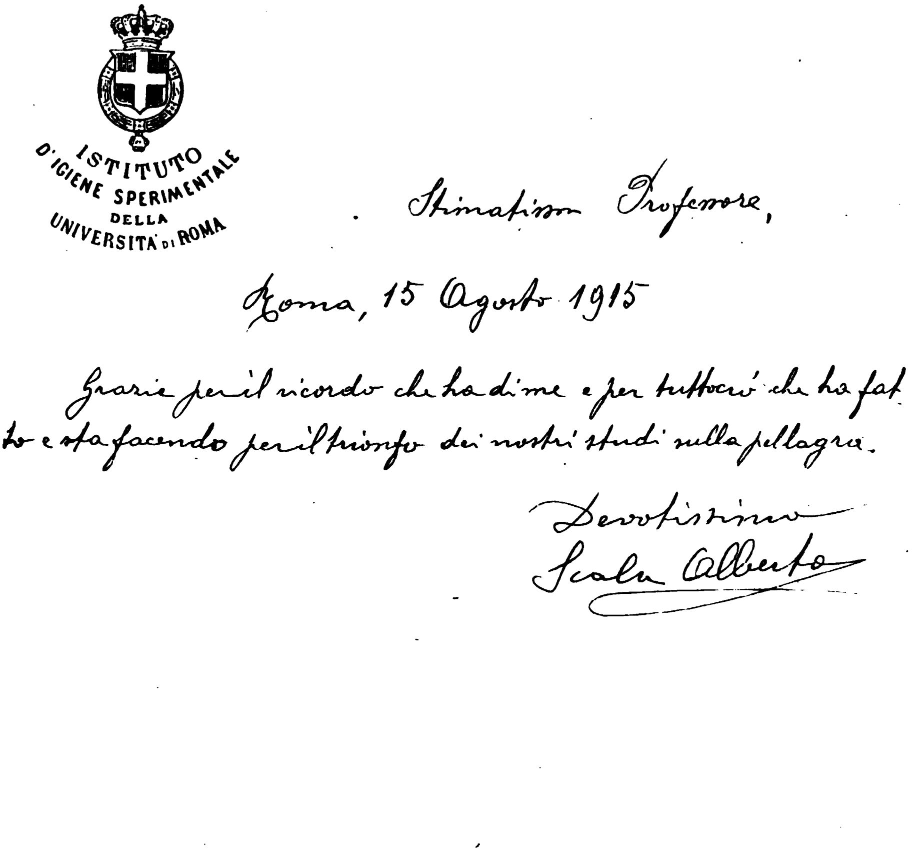


mativo noi potremmo spedirle
i clichés e quel quantitativo
di tavole che Ella sarà per
richiederci.

Mentre vivamente la ringrazio
di nuovo anche per il Collega
Scala mi è grato inviarle
i miei più distinti ossequi

Prof Giulio Alessandrini

Via Palermo 58 - Roma - (Italia)
R° Istituto d'Igiene -



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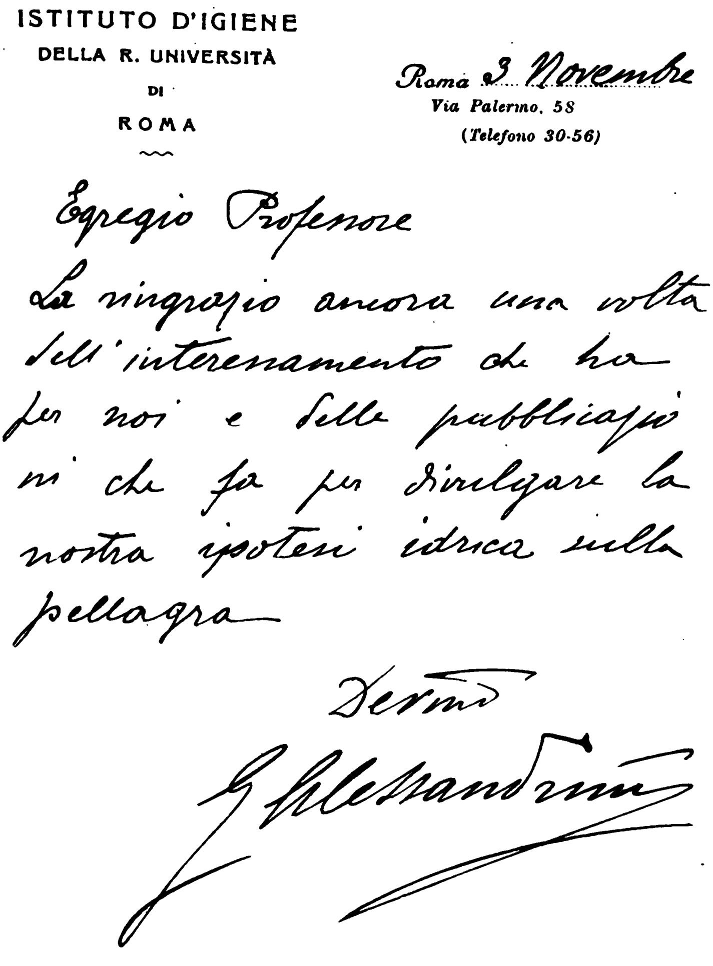
DELLA
UNIVERSITÀ DI ROMA

Stimatissimo Professore,

Roma, 15 Agosto 1915

Grazie per il ricordo che ha di me e per tuttociò che ha fatto e sta facendo per il trionfo dei nostri studi sulla pellagra.

Devotissimo
Scala Alberto



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Egregio Professore

La ringrazio ancora una volta dell'interessamento che ha per noi e delle pubblicazioni che fa per divulgare la nostra ipotesi idrica sulla pellagra —

Dev.mo

G. Alessandrini

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PART ONE

A NEW CONTRIBUTION TO THE ETIOLOGY AND PATHOGENESIS OF PELLAGRA.

PRELIMINARY NOTE.

The epidemiological research, made by one of us (Alessandrini) in 1909, at present leads to the conclusion that pellagra is *a disease strictly localized and contracted in a determinate zone where water is constantly drunk which originates in an argillaceous terrain, or flows through or stands on an argillaceous terrain.*

Through analogy with a certain parasitic disease of domestic animals and through certain casual coincidences of facts, it was supposed that the specific agent of pellagra was an animal parasite of the group of *Filariae.* On account of the first experiment of one of us (Alessandrini) instituted with monkeys, we were able to confirm the water origin of the disease and at the same time exclude parasitism.

In the meantime, the other of us (Scala) began to suspect that pellagra was determined by the action of a mineral substance which he had found, in special conditions of the water which was drunk in the pellagrous zone.

And following this new chemical indication, we instituted and brought to completion numerous experiments to the results of which we now alone refer, leaving the details to a monograph which we will publish later.

ETIOLOGY.

Pellagra, according to us, *is the effect of a chronic intoxication which is caused by silica in colloidal solution in water* *of determinate composition,* and therefore, may be also defined as *a disease caused by colloidal minerals.*

The clay is the prime cause of the sickness, whether it is rain water from the superficial strata or from the deep strata of the earth, the reagent is the same, which is a silicate of aluminum, one produced by hydrolysis, giving that form of silicic acid and aluminum hydrate, which, through the conditions such as obtain in this hydrolysis, are both able to pass into the water in the colloidal form. Since there is an incompatibility between silica and colloidal alumina, it is precipitated; therefore, there remains in the water only the excess of silica above the amount necessary for the precipitation of the alumina.

And the compound silica-alumina, not at all to be confounded with silicate of aluminum, forms a deposit and remains in part in a very fine colloidal suspension, which is the cause of the persistent opalescence which is frequently observed in the water drunk by the pellagrous.

Experimental Data.—The substances first used by us were: *The water of a pellagrous zone,* mixed in a small quantity of the food of the animals selected for experiment; *silica in colloidal solution and gelatinous silica,* the one by intraperitoneal and subcutaneous injection, the other by the mouth.

The animals of the experiment were rabbits, guinea pigs, dogs and monkeys.

We have results from them all always agreeing with a difference only in the greater or less time in which they were accomplished. An especially close relation exists between the celerity of action and the state of the silica in the water; between the intraperitoneal and subcutaneous methods and the method by the mouth.

In each method, the results obtained, whether through the symptomatology, or through the anatomo-pathological findings, macroscopic and microscopic, may be summed up in the following:

SYMPTOMATOLOGY.

The animals, in general, except rare cases of exceptional gravity, in which decline and death befell in a very short time, did not resent apparently the action of the substance administered; they remained about as usual, preserved their vivacity and tended to increase in weight. But all at once the hair lost its luster and fell in abundance from a proportionate scab; the falling commenced for the most part on the internal surface of the thighs, followed along the inner side of the narrow anterior, the flanks, the breast, the sides of the neck and extended from the nape of the neck to the tail; the eyes became dull, the appetite diminished, even almost entirely disappeared; intestinal disturbances supervened, which were more appreciable in the dogs and monkeys, less in the guinea pigs and rabbits. At first it was frequently diarrhoea, sometimes slightly bloody, alternating with costiveness, some had periods with normal feces and periods with feces small, hard, covered with a stratum of dense mucus, pale, sometimes streaked with blood.

The nervous disturbances which followed afterward were very diverse; an intense over-excitability was noted in some the guinea pigs, especially in accustomed quiet, would become agitated by nothing and upon the least noise scattered suddenly and ran as if mad, striking against obstacles which intervened.

Upon this period of excitement followed one of prostration, during which the animal falls as in a faint and its body is agitated by general tremors; only after a certain time it returns to the normal, only a little of the hyperesthesia remaining. On the other hand there may be a true nervous depression, in which the animal stands backed up in the most obscure part of the cage with the head down, concealed under the rack of the manger, insensible alike to stimuli and excitement.

In the more grave cases there is a spastic-paraparetic walk, with a tendency to retropulsion, complete paralysis of the posterior limbs, which may extend to the anterior. Often paralysis of the bladder is noted, and also of the vesical sphincter, which is manifest with retention and involuntary loss of urine. Meanwhile the weight diminishes, the emaciation becomes evident and often in marked contrast with the increased volume of the abdomen which appears distended and meteoric.

The animal arrived at this stage may die with clonic-tonic convulsions.

Cases have not been overlooked also in which death supervened without appreciable disturbance, although the animal had in appearance an aspect of perfect health.

PATHOLOGICAL ANATOMY.

A. Macrosopic Alterations.

Skin.—At the points where the hair had fallen from the scab we noted an erythema more or less intense and also a dense epidermic desquamation, which presented the form of bright white lamellae more or less large and thin. The underlying skin was hard, pale, slightly atrophic, and was less adherent to the subcutaneous tissue which was atrophied, for which reason the skin seemed detached and raised in tough folds. There were also more delicate points where inflammatory processes were established and were forming superficial sores, proceeding to vesiculation, which became confluent forming ulcers more or less extensive (monkeys). Cases are not wanting in which telangiectasic spots were observed.

The cutaneous alterations were more frequent in the animals with white hair and at the places where the skin was thin, (chest, inner side of leg, etc.); it was ordinarily wanting in those dogs which were kept in cages with closed sides, where the little light came only from above.

Subcutaneous Tissue and Muscles.—The panniculus adiposus was thin, the muscles pale, flaccid, dry, stuck together. This dryness of the tissues is found also in the serosa which for this reason appear more opaque; very rarely is there any peritoneal or pericardial fluid.

Internal Organs.—The heart was flaccid and ordinarily contained bright fluid blood.

The lungs were normal.

The liver had rather a normal appearance, frequently was hyperemic or also congested; it broke down, permitting blood to run out in abundance.

The spleen was rather hyperemic with the capsule roughened and the pulp very soft; more frequently it did not present anything abnormal.

The kidneys were for the most part congested and presented generally the aspect of the kidney with turbid new swelling.

The suprarenal capsules were always hyperemic and generally with cortical hemorrhage.

The principal alterations were of the character of systemic degeneration; the tongue was especially dry; the esophagus normal; the stomach, although void of food, was extraordinarily distended by the gas which was inclosed, and which was found even when the autopsy was made immediately after death. The walls of the stomach were always rather thin and at points becoming transparent and easy to lacerate with the minimum of traction. The mucosa generally presented only a hyperemia, in some a hemorrhage was found more or less extensive, according to the older data, but according to the most recent data, a hemorrhage which was not rare throughout the whole thickness of the walls. The pyloric region frequently by its thickness contrasted with the thin walls of the rest of the stomach.

The small intestine also was large, sometimes presenting throughout its whole length a very noticeable thinness, and becoming transparent so that one could see within the yellow liquid which filled it. Sometimes instead a zone is found more or less extensive, thin, transparent and distended, followed by another normal or even contracted, a guise in which the whole intestine assumes a moniliform aspect, which we were not able to verify in the control animals.

The contents of the intestine was soft, frothy and liquid, of a pale color or yellow. There was exfoliation of the mucosa from large tracts, leaving exposed a hyperemic, congested, hemorrhagic zone or scar.

Sometimes true ulceration was observed, varying in size, with overhanging edges.

The colon, which was often distended and full of gas, presented a hyperemic zone with scattering hemorrhagic points.

Nervous System.—The nervous system often did not present any change; but in some cases, especially when the cases had been of long duration, there was noted an injection or venous congestion of the meninges and of the cerebral substance, where also small hemorrhagic spots appeared.

The spinal meninges and the medulla presented injections and congestion.

The marrow of the long bones was of a reddish brown color.

B. Microscopic Alterations.

We are not skilled in the microscopic study of the lesions, lacking the necessary competency; and it was necessary to intrust the material collected to a person whose services we were able to utilize.

Altogether what we are able to give from a superficial examination is this: That in the skin was found a notable exfoliation of the stratum corneum, with leucocytic infiltration and with numerous eosinophiles under the corpus mucosum of Malpighi; that in the stomach hyperemia and hemorrhage were more or less extensive with a necrotic zone, and that in the intestine intense venous hyperemia was observed and exfoliation of the epithelium, as in the anatomical part appertaining to an animal killed intentionally; also that, as in the stomach, hemorrhage was noted more or less extensive and a necrotic zone.

This is the symptomatology, these are the changes macroscopic and microscopic which were observed in the animals of the experiment, which, while they have none of the particularly specific characteristics to be found in other intoxications, constitute the classical picture of pellagra, described by all the authorities, whenever, as in our cases, they present the characteristic triad at the same time.

It is observed: Silica is found in all potable water, in greater or less quantity, yet this is not the cause of pellagra, for if it were the whole world would be afflicted with the disease.

We answer that not all water is pellagrogenic, although it contains silica, as not all water containing oxygen dissolves lead, although the contained oxygen is the essential cause of the solution of this metal. For this reason we have found but one colloidal substances existing in the water; on the other hand, there is one colloidal substance which ought to pass through the water, the oxyhydrate of lead. And both are able to be influenced by certain neutral salts and mixtures of neutral salts in solution in the water. These, in the second case, arrest or favor the solution of the lead, impeding or favoring the passage through the water of the colloidal oxyhydrate, coming from the same solution; in the first case they inhibit or simply attenuate or increase the injurious action of the silica. And those salts which above all produce the beneficial modifications (except those whose action is little known) are the alkaline carbonates in general and the carbonate of calcium in particular, which exists and may exist in potable water, either alone or united to the others in different proportions.

After we had made the experiment on the animals of the action of colloidal silica in distilled water, we made an experiment on the action of the silica united with the carbonate of sodium, the carbonate of calcium dissolved in carbonic acid, the chlorid of sodium, the chlorid of calcium and gelatinous alumina. These substances were united with a solution of silica whenever they would not coagulate; they were injected separately but contemporaneously whenever they would coagulate.

From this second series of experiments we have the results which we summarize:

The chlorid of calcium and gelatinous alumina, although in very small doses, alike aggravated the action of the silica, especially in the guinea pigs and rabbits, hastening the appearance of the symptoms of the disease and shortening the course of the disease itself; the chlorid of sodium did not retard the action; the carbonates of sodium and calcium absolutely neutralized the action of the silica. So much so that the animals into which solutions of silica and the carbonates were injected at the same time not only did not present any symptoms of disease or sickness in life, but killed, after a long period of injections, did not show any changes characteristic of those already described.

PATHOGENESIS.

The solution of colloidal silica, injected under the skin of a dog which ate only common bread and drank Marcia water, and of which the urine was analyzed, collected every forty-eight hours, was the cause of a true *retention of sodium chlorid.* After five injections of one c.c. in which were contained 0.007114 grams of SiO_2 the chlorin in the urine fell off in quantity from a mean per cent of 4.79, decreased to 1.348, and after four more injections to 0.638, and the amount in forty-eight hours decreased from 0.798 to 0.167 and 0.051 respectively. At the same time the total solids in the urine were increased in quantity from a mean percentage of 39.66 after five injections to 96.98 and after four more injections to 144.90, and the total volume of urine in forty-eight hours from 6.852 to 12.025 and 11.592 respectively. These figures which we have collected from not a few analyses demonstrate not only that they had retention of sodium chlorid, under the action of the colloidal silica, but that, during the retention, the organism consumed not a little, and was indeed in extraordinary activity.

One or the other of these facts we have just indicated depends directly upon the silica, or the one depends upon the other; we are not able to decide with certainty; therefore, profiting by the facts noted, we are able to approach the truth, if we have not arrived at the truth already.

We do not believe that the retention of chlorin or more exactly of the chlorid of sodium is the first effect of the action of collodial silica upon the proteid substance of the tissues. In this case the silica acts like a diastasic substance which combines by a colloidal reaction, with chlorid of sodium and with the fixed proteid substance, substituting one or more molecules of water in colloidal combination with them:

$$[SiO_2]_m(\overset{-}{O}H'\overset{+}{H}')_n + (NaCl)_n \rightleftarrows [SiO_2]_m(\overset{-}{Cl}\overset{+}{Na}')_n + nH_2O$$

$$[SiO_2]_m(\overset{-}{Cl}'\overset{+}{Na}')_n + P_m(\overset{-}{O}H'\overset{+}{H}')_n \longrightarrow [SiO_2]_m(\overset{-}{O}H'\overset{+}{H}')_n + P_m(\overset{-}{Cl}'\overset{+}{Na}')_n \quad (1)$$

and that in reality silica combines with a certain affinity with chlorid of sodium, demonstrates the fact that when it coagulates the chlorid of sodium combines in a solution of determinate concentration, or else that the mixture, by combination with chlorid of sodium, does not combine in determinate volume and does not acquire diverse colloidal properties. Since colloidal silica exists in the tissues and chlorid of sodium is found in them, they have the same persistence and succession of reaction.

The fixation of chlorid of sodium must have a limit, above which it is not able to go; hence the periodic scarcity which we have in the urine, noted in the pellagrous, and demonstrated by us in a bitch, which was injected contemporaneously with a solution of colloidal silica and a 0.5 per cent solution of chlorid of sodium. And the bitch had a periodicity truly wonderful in the beginning, which was changed later and disappeared in the end. The quantity of sodium chlorid excreted increased again to the normal, to remain there or pass above the normal as in the pellagrous. This last point is only attained, for it is not a state possible to be maintained for more than 47 days by an animal in captivity as an experimental step in a chronic disease. The bitch was killed, presenting at autopsy the same lesions which we have already recorded.

This shows the fixation of the chlorid of sodium in the various tissues where the silica has penetrated, does not show the reason why this same chlorid of sodium, which is also a salt universally known and extolled for its virtue, is able to produce the disturbances and lesions described; on the other hand, it shows the primitive action of the silica; it does not show the secondary action.

Nevertheless, we believe we have succeeded also in this, recording the results of the experience of one of us (Scala) in collaboration with the lamented Signora Mengarini, an experience which we ought briefly to recount for the exact comprehension of what we set out afterward.

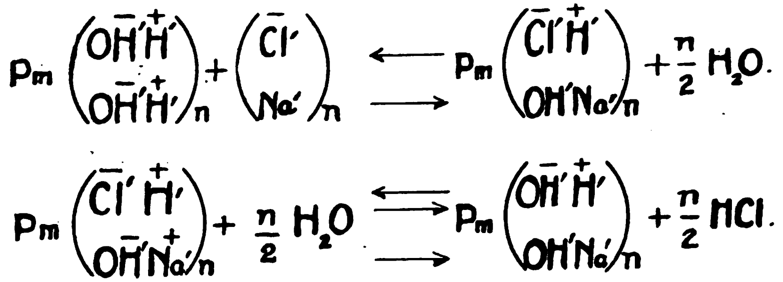
---

(1) $(SiO_2)m$ and Pm indicate the colloidal mixture of silica and of the proteid substance.

In 1906 it was shown that the red corpuscles of the blood and the Opaline, unicellular beings without a mouth, which live in the cloaca of the frog, are profoundly disturbed and rapidly die in an isotonic solution of chlorid of sodium in distilled water, and that they were not appreciably altered and remained alive when the isotonic solution of chlorid of sodium, instead of distilled water was prepared with the potable water of Rome. This led to the opinion that the chlorid of sodium alone; penetrated into the red corpuscles, or into the body of the Opaline, there producing such chemical conditions as to render life impossible. Therefore, it is not easy to penetrate the secret of the reaction which ought to take place between the chlorid of sodium and the protoplasmic substance of the cell, through the habitual belief that this neutral salt has a very simple office in our organism, as we speak of its presence, how it is introduced and that it is eliminated through the urine and through the other excretions and secretions. We have not observed the innumerable reactions which we were able to contemplate, once introduced into the organism, and instead have undertaken the part excreted from the same organism.

And it is possible to arrive at an explanation of the injurious effects of chlorid of sodium on the protoplasm of the living, having in mind the colloidal reaction, which ought to occur between the chlorid of sodium and the protoplasmic substance, from which through hydrolysis ought to be liberated *hydrochloric acid* or *the injurious substance.* We have been able easily to eliminate them by neutralization with an alkaline carbonate which accompanied the chlorid of sodium.

The formation of the mineral acid cannot only be demonstrated directly in the Opaline with micro-chemical reactions, but also it is possible to deduce the formula of the reaction which we report below, maintaining always the hypothesis stated by one of us (Scala), that the colloidal state of the material results from the combination of the material itself with ionized water.



$$P_m \begin{pmatrix} \overset{-}{OH'}\,\overset{+}{H'} \\ \overset{-}{OH'}\,\overset{+}{H'} \end{pmatrix}_n + \begin{pmatrix} \overset{-}{Cl'} \\ Na' \end{pmatrix}_n \underset{\longrightarrow}{\longleftarrow} P_m \begin{pmatrix} \overset{-}{Cl'}\,\overset{+}{H'} \\ OH'Na' \end{pmatrix}_n + \frac{n}{2} H_2O.$$

$$P_m \begin{pmatrix} \overset{-}{Cl'}\,\overset{+}{H'} \\ \overset{-}{OH'}\,\overset{+}{Na'} \end{pmatrix}_n + \frac{n}{2} H_2O \underset{\longrightarrow}{\rightleftarrows} P_m \begin{pmatrix} \overset{-}{OH'}\,\overset{+}{H'} \\ OH'Na' \end{pmatrix}_n + \frac{n}{2} HCl.$$

Hence, the combination of chlorid of sodium with the colloidal mixture would not be other than the continuation of the colloidal state, in which a part more or less large of the ions of water are substituted by the ions of the salt by which there is a true dehydration of the colloid. And in all of the animals of the experiment, declining quickly, in order that so important a fact should not escape, we demonstrated at the autopsy the characteristic and known signs of the pellagrous in the dryness of the flesh.

In this colloidal combination the group ClH behaves in hydrolysis in a manner different from the group OHNa; the first is more quickly hydrolyzed than the second, as one of us (Scala) has demonstrated in the combination sulfate of copper albumin, apparently from a tendency of compounds of this type to pass from sodio-acid-proteids to sodio-proteids or from cupro-acid-proteids to cupro-proteids.

With this understanding and with the facts acquired from the action of the silica on the animals and especially from the fixation of chlorid of sodium in the tissues, it seems to us to be possible to state that the injury produced by the colloidal silica is none other than secondary and in relation with the quantity of hydrochloric acid which is set at liberty by the hydrolysis. This, by contact with the tissues and with the proteid substance of the tissues themselves, provokes a reaction which we are obliged to say is of defense, in which the proteid substance is decomposed giving rise to ammonia which neutralizes the acid. Therefore, the large amount of extractive substance in the urine in contrast with the chlorin is, for the greater part, ammoniacal salts. These statements are only our own views and not directly determined, so as not to make the mistake of including the ammonia of elimination with that of fermentation. We have investigated, therefore, the difference between the sum of the ions, minerals determined in the urine, and the ash is greater in correspondence with the greater quantity of the extract.

But in this difficulty in which we have found ourselves in experimenting with animals, we were aided by the experiments of Moreschi, who was able to demonstrate that the fraction of nitrogen precipitable with phosfotungstic acid and easily liberated with phosforic acid, was larger in the urine of the pellagrous than in the healthy, or that in the one there was a greater quantity of nitrogen in the form of ammonia and of carbamic acid than in the other. And Moreschi has set in relation this ammonuria with an acid intoxication which he was not able to make out, but simply and plainly to be seen as we now demonstrate.

Therefore, pellagra has its own origin in a mineral acidosis, which becomes of greater amount than in conditions of health of the organism and which we are able to call necessary and beneficial, by the reaction between chlorid of sodium and proteid substance. This same acidosis becomes of higher grade because it is the colloidal silica which fixes chlorid of sodium in excess in the proteid substance of the various tissues, from which there is a greater liberation of hydrochloric acid and an acid intoxication.

With this we have kept an account and explained the exaggerated elimination of the chlorid of sodium in the pellagrous which was interpreted as demineralization and which is none other than the elimination of that chlorid of sodium which is increasingly fixed and of accumulated strength and which is continually accumulating in strength. Therefore, the point of equilibrium (for also in these reactions an equilibrium is not wanting) attains a height and becomes normal for the pellagrous as long as the cause exists which maintains this equilibrium. It is not possible, without an apparatus of platinum, to demonstrate the silica remaining in the tissues, contracting with the proteid substance a non-reversible colloidal combination, or if eliminated, after it has produced its action, is replaced by other which happens to be in potable water. Therefore, this demonstration should be of great interest, because in a case in which the silica is eliminated rapidly we ought to expect, with seriousness, to see an exaggerated emission of chlorid of sodium in the pellagrous, to a permanent deviation of the properties of the proteid substance caused by the silica, properties which persist to the end and which are a new cause not conducive to normality. It is not certain since this cause is found, that it is possible to cure the pellagrous; since it is also affirmed that the hyperchloruria of the pellagrous is improved when they change air and diet until it arrives at an entity rather physiological in the old pellagrins recovering in pellagrosaria, while the symptoms of the disease which afflicts them persist. In some way, by taking an exact count of them, the recent pallagrin should be distinguished from the pellagrin of long standing; the first has a possibility of cure by simple hygienic treatment; the second no longer has this possibility, because in his organism the alterations have arrived at such a gravity that they can no longer be modified, just as occurs in other diseases, among them in syphilis.

At this point arises a spontaneous demand for the administration of salt to the pellagrous, to more damage than benefit. The experiment with the bitch, which we have already recounted, demonstrates that there was not any acceleration of the disease and we observed a periodical step of retention and elimination ending in a pathological equilibrium, which did not arrive until after a time rather long and varied, in relation to the individuality and consequently to the means of resistance more or less at the disposal of the intoxicated organism.

Finally the recognized periodicity of pellagra, which is none other than the periodicity of one manifestation, as long as the disease lasts, is very well understood, the cause of the disease being known. In fact the mineral acid becomes as much more irritant in the parts exposed to the surrounding air and often to the direct rays of the sun, in proportion to the temperature of the same air and the rays of the sun, and in proportion to the concentration of the acid in the tissues. Because of this the erythema manifests itself in the beginning of spring only in those pellagrins in the tissues of whom the concentration of the acid is very great, and later, with the increase of the surrounding temperature, in those other pellagrins in whose tissues the concentration of acid is less.

With this do not exclude this manifestation, which it is possible to have also with irregularity, that a decrease of temperature almost always supplies an increased morbid activity and also an increased concentration of acid.

TREATMENT (CURA).

The pathogenesis being known, the treatment, if we should call it treatment, naturally depends upon it; an acidosis ought to be corrected by an alkali and this treatment we have followed with the dog, made sick by us and reduced to a bad state, by injecting a 5 per cent solution of trisodic citrate. We have seen the animals revive almost instantly and have seen the urine return to normal composition in sixteen days.

This same treatment we have followed with nine pellagrins of the territory of Gualdo Tadino, selected from those who in the preceding year had had manifestations quite grave. In these the treatment practically excluded any cause of error, in such a manner that any benefit which should be derived was not possible to be attributed to any other reason. The pellagrins were not moved from their habitations, there was no change in their food, nor diminution of labor. Daily injections of trisodic citrate were practiced at first with a dose of one c.c. of a 5 per cent solution, afterwards of a 10 per cent solution.

The result is indeed satisfactory; there was a diminution and cessation of the digestive disturbances (gas, eructations, weight, etc.), an increase of appetite, a disappearance of the vertigo, and of the sense of distrust of themselves, there is a notable increase of strength.

But these subjective symptoms might be assigned a relative value if the improvement did not appear in the aspect of the patient and was not confirmed by an increase in weight which was notable in all but one; by an increase in the vital force and especially by the fact that the cutaneous manifestations, already apparent in those not subjected to treatment, did not recur and have not yet recurred by any appearance in anyone.

Moreover, in one of our pellagrins treated, we have followed in the urine the ratio $\frac{\mathrm{Cl}}{\text{residue}}100$. We observed that at the beginning before the pellagrin was placed under any treatment, or there was any modification of the tenor of her life, the ratio was 27.18; placed in the hospital under conditions of observation the ratio decreased to 20.22; returned again to her own house and her accustomed surroundings the ratio was raised to 21.65. After a time, subjected to our treatment, but remaining in her accustomed surroundings and in her own home, the ratio decreased to 18.58. This demonstrates that the chlorin eliminated was diminished, taking account indirectly of the volume of the urine of 24 hours with the total quantity of substance in solution, not being able to obtain this volume directly.

PROPHYLAXIS.

Nothing remains now but to speak of the prophylaxis of pellagra, admitting always that the silica is the cause of pellagra. And also the prophylaxis follows naturally from our experience; therefore, if the colloidal silica is rendered inactive by the alkaline carbonates, and above all by the carbonate of calcium, pellagrogenic water can be rendered innocuous when in it there is immersed and permitted to remain permanently an excess of limestone in small pebbles, from which it is permitted to saturate.

And such a measure has an equal value in water lacking in alkaline carbonates or alkaline earths, where the quantity of these is small and insufficient to neutralize the injurious action of the silica, where there are electrolytes or mixtures of electrolytes in the water which increase the injurious action of the silica. Therefore, in three cases, we have added the antidote which was lacking or insufficient, or we have broken up with the new addition the injurious harmony between the silica and the electrolyte so that they change to their own properties. And the nature and the science of colloids tell us that this means never fails, because the calcium carbonate water is always harmless, and even beneficial; because quite often a small quantity of electrolytes or a mixture of electrolytes changes the colloids to properties of their own.

And one of us (Alessandrini) has already suggested the addition of broken limestone to the reservoirs of water in the pellagrogenic zone, to avoid the stirring up of the muddy bottom, in analogy with what was done with benefit in another pellagrogenic zone without knowing in reality that in such a manner they were doing a prophylaxis both rational and scientific.

We have desired to accompany this our study with analyses of water of pellagrogenic localities, as a demonstration more finished and convincing and to present also a type of pellagrogenic water. But the time is lacking, a labor long and accurate being necessary for this part alone, which we reserve for a time not remote.

In the meantime we desire that works of improvement, simple and of little expense, such as those suggested by us, be decided upon at once, so as to prevent the sickness of new persons, to improve the condition of those who have already contracted the disease, and also to give a desired satisfaction to us who have worked upon this subject many years with an ardor which comes from a knowledge of accomplishing a good work, and with a sacrifice which we alone know and which is known by those who work as we do.

And we desire the satisfaction given to us, not only by the simple establishment of the action of silica upon the animal organism, but by the establishment that silica is the true etiological agent of pellagra. For this we have commanded not only the experiments of the laboratory, but also the experience of treatment and prophylaxis, such as we have suggested and initiated, because together they are the results of all these experiments which ought to bring about the decision of this so grave a question, and, in a favorable case, the conversion of the skeptical and the decision of the doubtful.

The credit of these results is due to Professor Celli, our director, in that with a wise perception he desired that pellagra be studied in his Institute, using to advantage all the resources which he had assembled in the Institute. And the results of our study are such that, besides distinguishing pellagra, they mark a new conquest in the hygiene of potable water, which heretofore ought to have been analyzed in a manner more complete and otherwise indicated a conquest in the therapy of certain diseases, the origin of which is still as obscure as was that of pellagra.

Institute of Experimental Hygiene of Rome, May 22, 1913.

INSTITUTE OF EXPERIMENTAL HYGIENE OF THE ROYAL UNIVERSITY OF ROME.

A NEW CONTRIBUTION TO THE ETIOLOGY AND PATHOGENESIS OF PELLAGRA.

(MONOGRAPH (1) OF G. ALESSANDRINI AND A. SCALA.)

I.

The epidemiological research, initiated by one of us (Alessandrini) in 1909, and continued to date, leads to two fundamental conclusions:

1. That pellagra is not absolutely dependent upon maize alimentation;

2. That pellagra is a disease strictly localized and limited to a zone where the water drunk is in contact with an argillaceous terrain, either in whole or in part.

To these conclusions may be added the following: Because much pellagra exists where maize is not eaten; because there are regions in Italy and elsewhere (Molise, Campania, Basilicata, Liguria, Brazil, etc.) where an extraordinary use is made of maize, good, average and bad, in which pellagra does not exist; because in the same province, in the same communes, infected with pellagra immune zones are found, where the entire zone is identical in hygienic and economic conditions

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1. The present monograph, of which a preliminary note was communicated on the 25th of May, 1913, to the Royal Academy of medicine of Rome, is published under the auspices and with the assistance of the Pellagrological Commission of the Province of Rome, presided over by the Honorable Count Alberto Cencelli-Perti, senator of the Kingdom.

and where the prevailing alimentation is maize, and last, because pellagra has disappeared in many places where a new potable water has been furnished, and furnished in such a manner as to benefit existing conditions.

By analogy with certain parasitic diseases of animals (*Dermatorragia* from *Filaria haemorragica,* Railliet and *Piaghe estive* from embryos of *F. irritans* Riv.) which, like pellagra, present an acute periodic recurrence in summer with a remission in winter and have a progressive course and through certain casual coincidences of facts (finding the larva of *Filaridi* in the water and of certain ova on the skin of certain pellagrins) one of us (Alessandrini) thought that pellagra might be due to an animal parasite of the family *Filaridae.*

On account of a later experience with monkeys who were made to drink the water of Col d'Orto, a very pellagrous region in the commune of Gualdo Tadino, he became seriously doubtful of this supposition, and was even able to exclude it absolutely, confirming instead the water hypothesis and reenforcing the conclusions deduced from the epidemiological research. (See the research detailed on page 140-141).

Therefore, to determine the effect produced by the ingestion of a water coming from a locality where much pellagra exists, he did not hesitate, after bacteriologic failures, to incriminate the organic or mineral matter in solution or suspension in it.

But it was not easy to determine: First, if the active and deleterious was organic or mineral; later when this problem was resolved, it was not easy to distinguish between what is ordinarily found in common potable water.

Various reasons urged the exclusion a priori of organic material, because it was found in the water in very small quantity, because it was in such a state of oxidation as to have lost, in the case which we have observed, all deleterious action, and because it existed in all the waters, in whatever diverse quantity, in this same state of decay. On the other hand, no one heretofore suspected that the common mineral substances, although they exist in potable water, were able to provoke disturbances either immediately or a lingering decay. And it was only through the richness of information gathered concerning the character of the terrain from which the water came or upon which it reposed, which was drunk in pellagrous zones, that it was possible for one of us (Scala) to formulate an opinion that the silicic acid, free in the colloidal state, was able to produce a chronic intoxication, such as we observed in pellagra. Since there exists in reality, a relation between water and pellagra, the same relation ought to exist between silicious terrains or in general between a terrain and pellagra.

The silicious rock, which is most readily encountered in the terrestrial crust and which gives the water its silicia, is clay; the product of the slow decomposition of the feldspars and perhaps also of mica, so that from the complex forms of silicates of aluminum and potassium, they pass to the more simple form of insoluble silicate of aluminum and soluble carbonate of potassium, by the combined action of the water and the carbonic acid of the air.

Clay is rarely found pure in nature; ordinarily it is a mixture of silicate of aluminum, carbonate of calcium, carbonate of magnesium, of oxid of iron which gives it its red or yellow color, and of quartz sand.

The clay should contain extraneous substances in very small quantity, although it has lost its power to acquire such as chalk, marl or silico-calcareous earth. Also in the silico-calcareous earth it is possible to find both feldspar and mica not yet decomposed, talc $Mg_4Si_5O_7$—xH_2O which, in the pure state or mixed with quartz, forms a not indifferent part of the ridge of the Alps, serpentine $Mg_3Si_2O_7$—$2H_2O$ very frequently in the Alps and the Appenines and finally quartz in all its varieties and volcanic lava.

Rain water, which is natural distilled water, when it comes in contact with clay and with the other silicious rocks, or in other words, the fully disintegrated and later hydrolyzed, forms silicic acid and oxids of the alkaline earths, which are able to pass into the condition of carbonates, by the aid of the carbonic acid of the air, and also into silicic acid itself.

Silicic acid, as the facts demonstrate, passes easily into colloidal solution, on the contrary to alumina, which is an obstacle to electrolysis, is most readily coagulated and is antagonistic to the silica. And it is for this reason that in the water we have found a considerable quantity of silica and at the same time a very small quantity of alumina, so that, alone or in colloidal combination with silica, it forms a part of the bottom whence hydrolysis occurs. If this bottom is stirred up, together with the clay, at every agitation it is light and able to remain in the water in colloidal suspension, communicating turbidity or opalescence, as frequently observed in the water which is drunk in pellagrous zones.

In this study, conducted with purely scientific criteria, and founded entirely upon the knowledge of colloidal chemistry of one of us (Scala), we have been careful to determine first the action on the animal organism of a solution of colloidal silica in distilled water, containing the least possible quantity of extraneous substance; then of a suspension of gelatinous silica in distilled water; of a mixture of gelatinous silica with bran; with a solution of silica added to chlorid of sodium; of another added to chlorid of calcium; of another also added to carbonate of calcium and carbonate of sodium and finally of a suspension of gelatinous alumina in a solution of silica.

The colloidal solution of silica was prepared in the following manner.

Dissolve in about one liter of distilled water 20 grams of syrup of silicate of sodium; make the solution strongly acid with hydrochloric acid and dialyze in a dialyzer of animal parchment in a current of common water. The dialysis is considered complete when the liquid has entirely lost the acid reaction and when in it nitrate of silver produces no reaction. Thus obtained a colloidal solution of silica is always rather opalescent and sometimes coagulated, principally because of the small quantity of mineral impurity which acts as an excitant, favored by heat and the concentration of the solution relatively rather strong. And from this fact it may be assumed that the pure concentrate solution of silica which has long been dialyzed in distilled water has not coagulated spontaneously.

Silica in the gelatinous state is prepared by treating a concentrated solution of sodium silicate with small portions of hydrochloric acid to a distinct acid reaction. The coagulum is triturated in a porcelain mortar to render the mass uniform and is washed for a long time in distilled water, first by decantation, then on a filter, till the acidity and the reaction for chlorin disappear.

II.

EXPERIMENTS UPON ANIMALS.

The experiments were divided into many series, namely:

1. Subcutaneous and intraperitoneal injections of solution of colloidal silica and ordinary alimentation and with bran and herbs.
2. Subcutaneous and intraperitoneal injections of solution of colloidal silica and alimentation with corn meal and herbs.
3. Ingestion of a solution of colloidal silica and ordinary alimentation.
4. Injection of a suspension of gelatinous silica and alimentation with bran and herbs.
5. Injection of a suspension of gelatinous silica and alimentation with corn meal and herbs.
6. Ingestion of gelatinous silica and alimentation with bran and herbs.
7. Ingestion of gelatinous silica and alimentation with corn meal and herbs.
8. Injection of colloidal silica with the addition of chlorid of sodium and alimentation with bran and herbs.
9. Ingestion of gelatinous silica with the addition of chlorid of sodium and alimentation with bran and herbs.
10. Injection of colloidal silica with the addition of chol-

rid of calcium and alimentation with bran and herbs.

11. Injection of colloidal silica with alumina in suspension and alimentation with bran and herbs.

12. Ingestion of colloidal silica with alumina in suspension and ordinary alimentation and with bran and herbs.

13. Contemporaneous injection of a solution of colloidal silica and another of carbonate of calcium and alimentation with bran and herbs.

14. Contemporaneous injection of a solution of colloidal silica and another of carbonate of sodium and alimentation with bran and herbs.

15. Ingestion of water of the territory of Gualdo Tadino (a pellagrous zone) and ordinary alimentation and with bran and herbs.

16. Ingestion of water of the territory of Gualdo Tadino (a pellagrous zone) and alimentation with corn meal and herbs.

INJECTIONS AND INGESTION OF COLLOIDAL SILICA AND OF GELATINOUS SILICA.

Subcutaneous Injections of Colloidal Silica and Alimentation With Bran and Herbs.

This first series of experiments had for its object the knowledge of the action of the silica, in the colloidal state, upon the animal organism. And with this view we used a solution which contained SiO_2 0.7114 grams in 100.

The alimentation of the guinea pigs and rabbits was: in the morning, bran, in the afternoon, the leaves of cabbage or lettuce.

The alimentation of the dogs was: moistened bread and dough, cooked in water, containing salt and a little grease. For drinking, Marcia or Pia water, both of the best potable water of Rome.

1. Guinea pig, weight 350 grams.

This experiment was commenced May 11, 1912, injecting under the skin 2 c.c. of a solution of colloidal silica every two days.

The animal never seemed to rally from the treatment but withdrew from sight and on the 7th of June was found dead in the cage.

Duration of the experiment: 27 days.

Injections, 11.

Table of weights:

May 17, 1912, 300 grams.
May 26, 1912, 270 grams.
June 2, 1912, 250 grams.
June 7, 1912, 200 grams.

Autopsy. Pseudotuberculosis of rodents.

2. Guinea pig, weight 320 grams.

Injected under the skin, on alternate days, commencing the 16th of November, 1912, 2 c.c. of a solution of colloidal silica.

The animal, except a want of appetite, which it manifested in the last days of its life, did not present any disturbance.

Died the 10th of December.

Duration of the experiment, 23 days.

Injections, 9.

Table of weights:

November 28, 1912, 310 grams.
December 10, 1912, 225 grams.

Autopsy (made at once after death). Panniculus adiposus very thin; thin stratum of fibrinous exudate and slight hemorrhage at point of inoculation; diffuse thickening of the abdominal walls; heart flaccid,-pale; liver congested; lungs, spleen, kidneys and suprarenal capsules normal; intestine slightly hyperemic, a somewhat congested zone in the mucosa.

Stomach empty, with walls thin, transparent.

Cerebral and spinal meninges hyperemic. Nothing in the encephalon or the medulla. Marrow of the long bones reddish brown.

Bacteriological examination of the blood and exudate negative.

3. Guinea pig, weight 390 grams.

Injected on alternate days, 1 c.c. of colloidal silica. The experiment was commenced on the 16th day of November 1912.

After 20 injections, on the 7th day of January, 1913, on observing the animal closely it was observed that on the back and on the outside of the legs there were small hairless scabs. The skin was scaly and the scales, thin and clear, easily detached, disclosing a reddened skin. At the same time the animal was losing weight and lacking in nutrition.

On the 21st of January, after 27 injections, the animal died following repeated attacks of clonic-tonic convulsions.

Duration of the experiment, 66 days.

Injections, 27.

Table of weights:

November 28, 1912, 360 grams.
December 11, 1912, 400 grams.
December 30, 1912, 390 grams.
January 8, 1913, 370 grams.
January 21, 1913, 350 grams.

Autopsy. Fibrinous exudate at the point of injection; tissues excessively dry; subcutaneous thin.

Heart, lungs normal; spleen contracted.

In the intestinal cavity, deposits of fibrin and adhesions between all the organs.

Intense hyperemia of the entire intestine; the mucosa of the colon, the small intestine and above all of the duodenum, hemorrhagic in patches of greater or less extent. The walls of the intestine and also of the stomach were thin. Gastric mucosa with numerous punctate hemorrhages.

Liver congested; gall bladder full and much distended; kidneys flaccid and the two substances not clearly distinguished; suprarenal capsules congested with a somewhat hemorrhagic zone in the cortex.

Meninges and cerebral substance injected.

Marrow of the long bones reddish brown.

4. Guinea pig, weight 420 grams.

Injected on alternate days 2 c.c. of a solution of silica in the colloidal state.

Experiment commenced on the 11th day of December, 1912.

The animal, except a slight dejection and a marked loss of appetite, suddenly came to the day of his death, not seeming to have reacted to the treatment in any way.

Died on the night of the 15-16th of January.

Injections, 16.

Table of weights:

December 30, 1912, 380 grams.
January 8, 1913, 320 grams.
January 16, 1913, 275 grams.

Autopsy. Very notable emaciation; tissues dry; muscles pallid, sticky; exudate organized at the points of injection, especially on the left.

Complete absence of pericardial and peritoneal liquid, serosa opaque, dry and adherent.

Throughout the intestinal tract coagula of fibrin were observed and consequent adherence to the abdominal wall.

The heart flaccid, lungs somewhat congested; spleen congested; liver congested; gall cyst full, greatly distended; kidneys covered with a coagulum of fibrin, congested, with a hemorrhagic zone in the cortex; suprarenal capsules hyperemic; bladder full and distended; intestinal vessels injected and mucosa with hemorrhagic spots throughout its whole length, more especially in the duodenum, ileum and small intestine.

Stomach empty, flaccid and walls very thin.

Intense hyperemia of the meninges, which presented roughness and opacity.

Venous injection of the cortical substance of the brain, where an extensive hyperemic zone was noted.

Marrow of the long bones reddish brown.

5. Guinea pig, weight 460 grams.

The first subcutaneous injection of 1 c.c. of a solution of colloidal silica was made on the 13th of December.

Without apparent disturbance, on the 26th of December the guinea pig died after having received six injections and weighing 380 grams.

Autopsy (at once after death): Gelatinous edema at the point of injection and fibrinous exudate on all the abdominal organs. Muscles pale, flaccid; heart, lungs and spleen normal; liver congested, friable; kidneys flaccid, without distinction between the two substances; suprarenal capsules hyperemic.

Discrete venous injection of the whole intestinal tract, so that the mucosa of the small intestine presents a notable hyperemia.

Stomach full, mucosa hyperemic.

Venous injection of the meninges and slight hyperemia of the cerebral substance which also is edematous.

Marrow of the long bones of the type of red bone marrow.

6. Rabbit, weight 1,800 grams.

The experiment was initiated on the 16th of November, 1912, by injecting on alternate days, 2 c.c. of a solution of colloidal silica in the subcutaneous tissue.

During the first few days, the rabbit seemed to resist the effect of the substance injected, but after only 6 injections, manifested a weakness and a notable loss of appetite. At the eighth injection it seemed that the urine was very scant and on the 11th of December, after 11 injections, it was observed that there was not only an involuntary emission of a small quantity of urine, but also paralysis of the posterior limbs.

At that time the injections were suspended yet the weakness was progressive, so that on the 16th day there was paralysis of the anterior limbs and on the 18th day paralysis of the muscles of the left side of the neck was noted with torsion of the head to the right.

The animal was found dead on the morning of the 20th day of December.

Duration of the experiment, 34 days.

Injections, 16.

Table of weights:

November 28, 1912, 1,780 grams.
December 11, 1912, 1,770 grams.
December 20, 1912, 1,560 grams.

Autopsy. Very considerable emaciation; tissues arid, adherent, opaque, rather parchment like; muscles arid, flaccid, very pale.

Slight fibrinous exudate at the points of injection, under the skin, under the serous layer of the abdominal walls; heart flaccid, with little blood normally coagulated. Lungs dry; spleen normal; liver congested with a very small nodule of coccidiosis; gall bladder turgid; kidney of soft consistency and on cutting presents the appearance of a kidney with cloudy swelling; suprarenal capsules normal. Intestinal tract dry, adherent, thin and transparent, especially the secum; mucosa intensely hyperemic with a zone of punctfiorm hemorrhage; stomach empty with a mucosa here and there specked with hemorrhagic points.

Venous injection of the meninges and a notable hyperemia of the cerebral substance.

Marrow of the long bones reddish brown.

7. Rabbit, weight 1,680 grams.

Experiment initiated the 20th day of December, by injecting 2 c.c. of a solution of silica in the peritoneal cavity.

The rabbit, during the first days, ate with appetite and increased in weight.

After about twenty days the hair became rough and opaque and fell out abundantly.

The underlying skin desquamated in thin clear scales and appeared very red.

The animal began to eat sparingly and sometimes left the bran untouched.

At the same time the falling of the hair was localized on various parts of the body in large symmetrical patches.

Contemporaneously a notable emaciation was observed.

The eyes became dull and sunken. The respiration became rapid.

Removed from the cage (January 25) it was noted that the walk was disturbed; not able to stand on the ground with its front feet, which were turned inward. At the same time the posterior limbs were straight, rigid, in spastic paresis. The failure of appetite increased, alvine discharges became rare and the animal was found dead on the 10th day of February.

Duration of the experiment, 53 days.

Injections, 23.

Table of weights:

December 30, 1912, 1,750 grams.
January 22, 1913, 1,580 grams.
February 10, 1913, 1,300 grams.

Autopsy. Numerous hairless spots over the whole body, which had become recovered with normal hair only on the head, on the extremities of the anterior and posterior limbs and on a circular zone on the back. The regions of the flanks, the inguinal, the sacral were entirely denuded. The inner side of the thighs was entirely nude as was also the dorsal side of the hind legs (Fig. 1).

Subcutaneous thin, somewhat dry; muscles flaccid, pale, opaque; serosa opaque, dry; heart flaccid; lungs and spleen normal; liver congested; kidneys and suprarenal capsules hyperemic.

Tract of the small intestine markedly injected; intense hyperemia and hemorrhagic spots throughout the mucosa of the duodenum and small intestine; stomach empty with a little liquid mucus and the mucosa congested with a hemorrhagic stippling.

Meninges and cortical substance of the brain hyperemic.

Marrow of the long bones reddish brown.

8. Rabbit, weight 1,320 grams.

On the 23rd day of December, 1912, injected on alternate days, 2 c.c. of a solution of silica in the subcutaneous connective tissue.

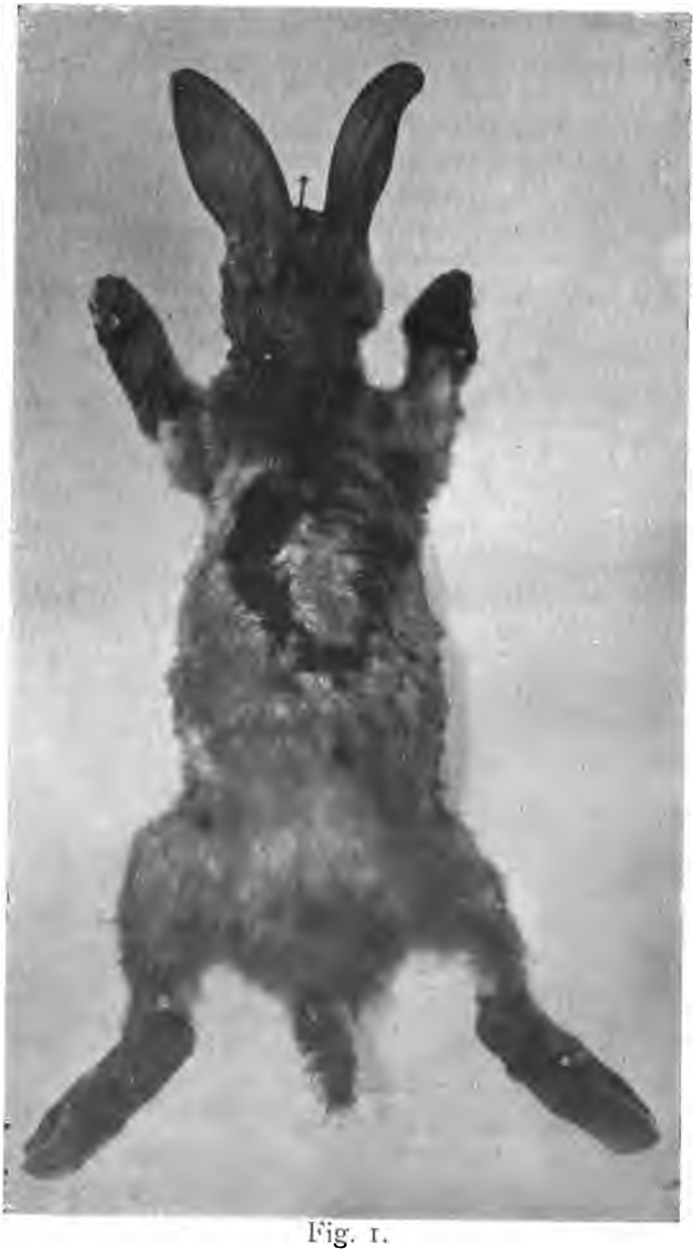


Fig. 1.

Without presenting any apparent disturbance, died on the night of the 28th day.

Duration of the experiment, 5 days.

Injections, 2.

Weight of the dead animal, 1,280 grams.

Autopsy. All of the organs and tissues normal. There was only noted one slight fibrinous exudate in the peritoneum and an intense hyperemia of the whole intestinal tract and the stomach. The mucosa of the intestine also presented a hyperemic zone and small punctiform hemorrhage; in the stomach three small hemorrhages of recent date in the pyloric region.

9. Rabbit, weight 1,430 grams.

Injected subcutaneously commencing on the 28th of December, 1912, on alternate days, 2.c.c. of a solution of colloidal silica.

The animal for a long time, did not present any disturbance; only at the end of March did we commence to note hairless spots on the sides of the body and on the back.

At this time, the rabbit withdrew from sight, refused food, and defecated at periods more or less long (from 2 to 5 days).

On April 20th on taking the animal from the cage, for cleaning, it was noted that it lost urine involuntarily. The hair on the flanks and the back of the neck had fallen almost entirely and all of the inside of the legs was bare where the skin presented a red color.

Refused food entirely the last three days before death, which occurred on the 7th of May.

Duration of the experiment, 131 days.

Number of injections, 56.

Table of weights:

January 8, 1913, 1,450 grams.
January 22, 1913, 1,490 grams.
February 7, 1913, 1,360 grams.
February 26, 1913, 1,310 grams.
March 26, 1913, 1,285 grams.
April 22, 1913, 1,200 grams.

May 7, 1913, 1,030 grams.

Autopsy. Alterations of the skin already noted in life. Subcutaneous thin, muscles pallid, flaccid, adherent; serosa dry, parchment like; heart flaccid, containing a little fluid blood.

Lungs normal; liver congested with one nodule of coccidiosis in the process of calcification; gall bladder full; spleen normal; kidneys and suprarenal capsules hyperemic. The intestinal tract distended by a great quantity of frothy, yellowish liquid or by feces which were stagnant. There was venous injection of the mucosa especially of the duodenum and the small intestine interspersed with a hemorrhagic zone.

Stomach empty with very thin walls, less in the pyloric region, where there was a thickening of about 7 millimeters; gastric mucosa congested, with numerous hemorrhagic spots of old date.

Meninges injected; cortical substance of the brain hyperemic, soft.

Marrow of the long bones reddish brown.

10. Dog, weight 5,300 grams (male).

Commenced the experiment on the 20th day of December, 1912. Injected into the animal daily 2 c.c. of colloidal silica under the skin alternately on the right and on the left side.

After about 15 injections, on the 22nd of January, the weight had decreased to 4,800 grams and had commenced to note a rapid falling of the hair.

The depilation was not slow and was localized in the region of the elbows and extended from the paw (hand) to the axilla.

At this time the dog was completely isolated (January 31), withdrew into the most obscure and sheltered corner of the court and tried to bite anyone who came near. Feared that he was infected with rabies and kept him separate from the others, under observation, suspending the injections. The tendency to bite disappeared after five or six days, also being inert and selecting places more isolated, began again to practice the injection on the 7th of February, and so continued for a similar time.

In the meantime on the 14th of February profuse lachrymation was noted and a very grave *cherato-iritis* appeared in the right eye. The left also was affected but less intensely.

This ocular lesion made him confused and discouraged; but he permitted to make the daily injections.

On the 28th of February there was a healing of the ocular lesion; but the prostration and isolation continued. The weight decreased to 4,200 grams.

The depilation extended to the nose. An intense diarrhoea supervened (March 12) and with it greater prostration. The dog dug a deep hole by a rock and remained in it all the rest of the day, without moving except to take his food. A notable constipation succeeded the diarrhoea accompanied by tenesmus. The weight the while continued to decrease and reached 3,850 grams on the 22nd of March. The prostration was then notable and a new difficulty arose in making the injections, since the dog tried to bite again, whenever anyone scarcely approached; so that on the 18th of April it was no longer possible to come near. It was killed on April 24th, the weight having decreased to 3,380 grams.

Duration of the experiment, 122 days.

Number of injections, 48.

Autopsy, (made at once after death). Depilation of the region of the shoulder, of the axilla and the nose with great exfoliation of epithelium corneum and intense hyperemia of the underlying skin.

The subcutaneous discretely conserved; muscles somewhat pale; heart flaccid; lungs and spleen normal; liver somewhat congested; kidneys and suprarenal capsules hyperemic.

Stomach and intestine empty but enormously distended with gas and containing a foamy yellow liquid; gastric and intestinal mucosa intensely hyperemic with numerous hemorrhagic spots; meninges and cortical substance of the brain distinctly hyperemic; marrow of the long bones dark red.

11. Dog, weight 4,350 grams (male).

On the 7th of January, 1913, commenced to inject into the dog each day two cubic centimeters of a solution of silica in the subcutaneous tissues.

The injections were continued uninterruptedly until the 17th day of January, on which day they were suspended to follow the modifications which took place in the urine. The weight on this day was 4,340 grams.

Resumed the injections the 31st of January. The animal sensibly resented the treatment, became weak, miserable, emaciated and drowsy. There was an abundant falling of hair without any special localization. On the 20th of February the weight had decreased to 4,100; there was almost no nutrition and very great prostration, to which was also added a discrete sanguinous diarrhoea.

At this time it was decided, also, to inquire into the action of the urine, under the administration of trisodic citrate and so on one side 2 c.c. of colloidal silica were injected daily and one the other 2 c.c. of a 10 per cent solution of the citrate were injected.

At once the animal reacquired its appetite; the diarrhoea ceased, and little by little his vivacity and weight returned. After six days of treatment, the weight increased to 4,370 grams and on the 8th day of March, after 15 days of treatment, we saw the weight increased to 4,480 grams and after 12 days to 4,590. Meanwhile all disturbance ceased and the animal lively and cheerful was set at liberty on the 26th day of March, having reached 4,850 grams in weight.

Then the injections of citrate were discontinued as well as of the silica, which later was resumed on the 7th of May in the proportion of 2 c.c. each day (weight 5,100 grams).

Then the animal seemed at once to resent the effect of the injections, then after scarcely eight days, there commenced an abundant *defluvium* localized especially in narrow strips, which at once became almost completely denuded. The dry epithelium became detached in the form of thin clear scales which easily fell off and left a view of smooth skin, intensely hyperemic, atrophic.

These localized alterations became general: The dog became wretched, depressed, refused food, whined. The hair became harsh, rough; a rise of temperature supervened and a tremor of the whole body. There was also from time to time a mucous diarrhoea with some streaks of blood.

On the 12th day of June the animal was killed, its weight in 35 days had decreased from 5,100 grams to 4,180.

Autopsy (made at once after death). Symmetrical depilation quite complete over all four legs, the skin was covered with scales easily detachable leaving in view an underlying stratum intensely hyperemic.

Subcutaneous tissue discretely preserved; muscles pale, dry, adherent; serosa dry; heart flaccid; lungs and spleen normal; liver congested; kidneys and suprarenal capsules hyperemic.

Intestine markedly injected with extensive hemorrhagic zone of large spots in the mucosa.

Stomach empty of food and full of greenish, frothy mucus; gastric mucosa congested with a hemorrhagic zone, especially in proximity to the pylorus; meninges and cortical substance of the brain markedly injected; marrow of the long bones dark red.

Intraperitoneal Injections of a Solution of Colloidal Silica and Alimentation With Bran and Herbs.

12. Guinea pig, weight 350 grams.

Commenced the experiment on the 11th day of May, 1912.

Injected every two days 2 c.c. of colloidal silica into the peritoneal cavity.

The guinea pig succumbed on the 29th of June, not having exhibited appreciable symptoms, except a little slowness in eating and a slight loss of weight.

Duration of the experiment, 49 days.

Injections, 19.

May 26, 1912, 330 grams.
June 2, 1912, 340 grams.

June 14, 1912, 325 grams.
June 25, 1912, 310 grams.
June 29, 1912, 290 grams.

Autopsy. Edematous infiltration at the point of injection; panniculus adiposus, thin; muscles flaccid, pale.

Pleural and pericardial liquid very scarce.

Fibrinous exudate on the walls of the intestine and the spleen.

Heart and lungs normal; liver congested.

Intestinal tract injected and in the mucosa here and there hemorrhagic spots; walls of the intestine very thin, transparent. The stomach with walls so thin that they permitted one to feel and to see the small amount of material contained in it.

The spleen somewhat enlarged and congested; kidneys and suprarenal capsules congested; meninges injected; surface of the brain hyperemic. Marrow of the long bones a dull red.

13. Guinea pig, weight 360 grams.

On the 16th of November injected one cubic centimeter of a solution of colloidal silica in the peritoneal cavity and so continued on alternate days.

After 20 injections commenced to observe a notable falling of hair, especially on the back, where was noted also a zone entirely bare which left a view of glistening skin, thin, clear and slightly hyperemic. On the 22nd of January the guinea pig manifested prostration, lay hidden on the bottom of the cage under the manger, rolled up with its hair erect and would not eat.

The prostration increased until the day of its death, which occurred on the 1st of February.

Duration of the experiment, 76 days.

Injections, 32.

Table of weights:

November 28, 1912, 360 grams.
December 11, 1912, 340 grams.
December 30, 1912, 330 grams.

January 8, 1913, 320 grams.
January 21, 1913, 330 grams.
February 1, 1913, 260 grams.

Autopsy. Notable emaciation; hairless spots on the back, on the flanks and on the inner sides of the limbs.

Subcutaneous thin; tissues arid, muscles pale.

Organized exudate at the points of injection, especially on the left; very little pericardial and peritoneal liquid.

Coagula of fibrin throughout the intestinal tract, where in contact with the walls of the abdomen already adherent.

Heart, lungs, spleen normal; liver somewhat congested; gall cyst enormously distended; kidneys congested, suprarenal capsules hyperemic; bladder full.

Throughout the intestinal tract and the walls of the stomach subserous hemorrhagic spots, which are also found, in correspondence in the intestinal and gastric mucosa.

Intense hyperemia of the meninges and of the cerebral cortex.

Marrow of the long bones brownish red.

14. Guinea pig, weight 340 grams.

Commenced the experiment the 16th day of November, 1912, by injecting, on alternate days, in the peritoneal cavity 2 c.c. of liquid.

The guinea pig presented no symptoms worthy of note during the whole period of the experiment, except a discrete decline.

Died during the night of the 19th of December.

Duration of the experiment, 32 days.

Injections, 13.

Table of weights:

November 28, 1912, 300 grams.
December 11, 1912, 250 grams.
December 16, 1912, 200 grams.

Autopsy. Subcutaneous very thin; muscles very pale; nothing at the point of injection; diffuse adhesion between the parietal and visceral serosa, by a thin stratum of fibrin.

Heart flaccid; lungs somewhat congested; spleen and liver normal; kidneys hyperemic; suprarenal capsules normal.

Intestinal tract injected; small intestine, full of frothy greenish yellow liquid and the walls very thin and transparent; stomach with a little liquid and the walls normal.

Mucosa of the small intestine hyperemic with a hemorrhagic zone; mucosa of the secum intensely hyperemic, with a large hemorrhagic spot at its beginning; gastric mucosa normal.

Meninges injected; cerebral cortex hyperemic; marrow of the long bones raspberry red.

A streaking of the marrow of the bones was noted.

Numerous blood corpuscles in vacuole degeneration; abundant basophile granulation and also many with rings of Dehler (bodies of Cabot).

Numerous normoblasts and more numerous also the many megaloblasts with basophilic granulation.

Mononuclear leucocytes very abundant; lymphocytes abundant; polynuclear neutrophile leucocytes scarce; abundant eosinophiles and eosinophilic myelocytes.

15. Guinea pig, weight 420 grams.

Commenced the experiment the 13th of December and injected 1 c.c. of solution of colloidal silica in the peritoneum.

After 18 days and seven injections on the 30th of December the animal died, without having presented anything of note in life, nor a diminution of weight.

Autopsy (made at once after death). Slight gelatinous edema at the point of injections and fibrinous exudate throughout the intestinal tract. Muscles somewhat pale; subcutaneous well preserved; heart, lungs and serosa normal; blood normally coagulated; spleen congested; kidneys flaccid without distinction of the two substances; suprarenal capsules hyperemic in the medulla; liver congested, gall cyst full.

Hemorrhagic spots in the walls of the stomach and in the intestinal mucosa, especially in the mucosa of the small intestine; an extensive hemorrhagic spot was noted on the abdominal face of the diaphragm.

Meninges rough, injected, cortical substance of the brain somewhat hyperemic.

Medulla of the long bones raspberry red.

16. Guinea pig, weight 420 grams.

Commenced the experiment the 20th day of December, by injecting, on alternate days in the peritoneum, 2 c.c. of a solution of colloidal silica.

The guinea pig presented nothing abnormal, except a marked progressive emaciation and a state of prostration and loss of appetite which were manifest in the last days of life.

Died on the night of January 31.

Duration of the experiment, 41 days.

Number of injections, 18.

Table of weights:

December 30, 1912, 350 grams.
January 8, 1913, 320 grams.
January 22, 1913, 340 grams.
January 31, 1913, 260 grams.

Autopsy. Subcutaneous very thin, muscles pale, arid, flabby.

Nothing at the point of injection. Adherence between the various organs and between the visceral and parietal serosa by a thin stratum of fibrin.

Heart flaccid; spleen and lungs normal; liver, kidneys and suprarenal capsules hyperemic.

The intestinal tract intensely injected with the mucosa, especially of the duodenum and small intestine, sprinkled with numerous punctiform hemorrhages; stomach with the most intense and diffuse hyperemia of the mucosa.

Meninges markedly injected; cerebral cortex very hyperemic and soft.

Marrow of the long bones reddish brown.

17. Rabbit, weight 1,700 grams.

Commenced the experiment the 16th of November, injecting into the peritoneum 2 c.c. of a colloidal solution of silica.

At the time of the 6th injection began to notice a very marked emaciation and a notable prostration accompanied by loss of appetite.

After the ninth injection, it presented oliguria accompanied by defecation of dry, hard, opaque feces. The walk confused by partially dragging the hind parts which later became completely paralyzed. At the same time also there was paralysis of the vesical sphincter with continuous involuntary loss of urine.

The animal died the 13th day of December.

Duration of the experiment, 29 days.

Number of injections, 10.

Table of weights:

November 28, 1912, 1,600 grams.
December 11, 1912, 1,530 grams.
December 13, 1912, 1,460 grams.

Autopsy. Notable emaciation, and hairless spots on the internal side of the thigh and the forelegs, where the skin appeared intensely hyperemic.

Subcutaneous thin; exudate at the point of injection on the left side.

Heart, lungs and spleen normal; liver congested; kidneys somewhat congested; suprarenal capsules hyperemic with slight punctiform hemorrhage in the cortex.

Intestinal tract markedly injected with venous congestion and here and there hemorrhagic spots in the serosa. The mucosa of the duodenum, of the small intestine and of the colon, was throughout its whole length, sprinkled with a hemorrhagic zone which resembled marbling.

Stomach full of undigested food. This remained compact and when detached from the walls was covered with a dense stratum of mucus, white, opaque. The gastric mucosa was congested and at one point in the greater curvature there was a hemorrhagic spot of the size and form of beech mast.

Meninges much injected; cortical substance of the brain hyperemic, easily broken.

Marrow of the long bones dark brownish red.

Nothing in the bacteriological examination of the blood and the exudates.

18. Rabbit, weight 2,000 grams.

Injected on alternate days, 2 c.c. of a solution of colloidal silica in the peritoneal cavity, commencing on the 16th day of December, 1912.

The animal resented at once the action of the silica, became very dejected in the cage and ate very little.

Died the 8th of January.

Duration of the experiment, 24 days.

Number of injections, 10.

Table of weights:

December 30, 1912, 1,890 grams.
January 7, 1913, 1,750 grams.
January 8, 1913, 1,700 grams.

Autopsy. Marked venous injection of the intestinal tract, which here and there was covered with a thin fibrinous exudate. Mucosa of the duodenum and of the small intestine with large hemorrhagic spots, so that it resembled marbling.

Stomach empty of food, with a small amount of greenish, foamy liquid; gastric mucosa strongly congested, of a violet color .

The other internal organs were apparently normal. Brain and meninges apparently normal.

Marrow of the long bones dark red.

19. Rabbit, weight 1,540 grams.

Commenced the experiment on the 16th of December, injecting into the peritoneum on alternate days 2 c.c. of a solution of colloidal silica.

The animal seemed to react to the injection at once. A few days before its death it was noted that it did not defecate as usual and that it urinated less than usual; it was prostrated and poorly nourished.

Defecation and urination were completely suspended 3 days before death, which occurred on the 17th day of February, 1913.

Duration of the experiment, 63 days.

Number of injections, 27.

Table of weights:

December 30, 1912,	1,510 grams.
January 8, 1913,	1,550 grams.
January 22, 1913,	1,570 grams.
February 7, 1913,	1,550 grams.
February 17, 1913,	1,520 grams.

Autopsy. Hairless spots on the skin of the back; subcutaneous thin; muscles flaccid, dry, pale.

Heart, flaccid, empty, with red fluid blood; complete absence of pericardial and peritoneal fluid; liver congested; lungs and spleen normal; bladder full and much distended; kidneys congested and the suprarenal capsules with hyperemic cortex.

The intestinal tract enormously distended with ingested materials and fetid gas; rectum full and distended with dry hard feces.

Mucosa of the small intestine, throughout a long tract, intensely congested with an extensive ulcerated zone and numerous hemorrhagic spots.

Stomach full of alimentary material and fetid gas, which did not distend the walls, although they appeared thin and transparent; in the mucosa were old hemorrhagic spots and a hyperemic zone.

Meninges and cortical substance of the brain hyperemic.

Marrow of the long bones brownish red.

20. Rabbit, weight 1,930 grams.

Commenced the experiment on the 20th of February, 1913, and injected into the peritoneum on alternate days 2 c.c. of a solution of colloidal silica.

Except an abundant falling of hair, which commenced at once after the 5th injection and which, increasing from day to day, was localized on the flanks, the back and the neck, the animal remained well, at least in appearance, until about the end of March.

From this time it commenced to withdraw from sight. The emaciation was notable, failure of appetite followed and with it great prostration. The animal always remained hid under the manger, refusing the light. Scarcely reacted to any stimuli, and urged to walk, went backward.

On the 18th of April, made to leave the cage, it was noted that the retrogression was very marked and, however urged, it was unable to move forward. The front legs were in spastic paresis, the eyes were fixed, inert; the hair dry and harsh.

The animal absolutely refused its food and died on the 26th of April.

Duration of the experiment, 66 days.

Number of injections, 29.

Table of weights:

March 10, 1913, 1,950 grams.
March 26, 1913, 1,900 grams.
April 22, 1913, 1,710 grams.
April 26, 1913, 1,630 grams.

Autopsy. Cutaneous lesions noted during life.

Subcutaneous tissue thin, dry, adherent; muscles opaque, flaccid, pale; serosa, hard, opaque.

Slight fibrinous exudate throughout the intestinal tract, so that they were somewhat adherent to each other.

Heart flaccid; spleen normal; liver, kidneys and suprarenal capsules hyperemic. Lungs congested.

The intestinal tract injected with the mucosa hyperemic and here and there sprinkled with very numerous punctiform hemorrhages.

Stomach with walls very thin, full of a greenish frothy liquid, with the mucosa intensely hyperemic, and with a hemorrhagic spot, if very recent date, in proximity to the pylorus.

Meninges strongly injected. Cerebral cortex very hyperemic.

Marrow of the long bones brownish red.

RECAPITULATION.

Colloidal silica, injected under the skin and into the peritoneal cavity of guinea pigs, rabbits and dogs, is very harmful; since in a time more or less long, it has caused the death of all.

The intoxication presents a picture well determined and manifest, with decline, failure of appetite and falling of hair from symmetrical spots; sometimes with spastic paresis and also paralysis, which is able, in addition to this picture, to be extended to the sphincters and expulsive muscles.

At autopsy the lesions of the stomach and intestine were constant, and consisted principally of a thinning of their walls and in the presence of a hyperemic zone, or a hemorrhage of the mucosa and also of the serosa. In a far greater number of cases the following condition was found: hepatic congestion, fullness of the gall bladder, and hyperemia more or less intense of the meninges and of the cortical substance of the brain, which was also frequently soft and edematous.

The marrow of the long bones was always brownish red or darker.

Examination of the blood, made only in certain cases, revealed the characteristics of a grave anemia.

These experiments therefore meet fully the objection that the silica, as a colloid, is not able to pass through the cellular membranes and to be diffused, because the lesions produced by it are found in the organs far removed from the point of inoculation. But, independent of these facts, the objection has no scientific basis, because the mobility of colloids in living organisms provides the innumerable colloidal reactions of the superficies because they form combinations more readily in the state of molecular dispersion and are able to pass through the membranes more readily than those which are not composed of primitive colloids.

Subcutaneous Injections of Colloidal Silica and Alimentation With Corn Meal and Herbs.

Having established that the silica, in the colloidal state, intoxicates the animal organism, we desired to see if alimentation with maize concurred in any manner to aggravate or to alleviate this intoxication. And therefore for the animals in the experiment for the bran we substituted an equal quantity of corn meal, maintaining always the same ration of herbs. For we judged that as water was indispensible, so also was cellulose, which in herbivorous rodents is an excitant of the peristaltic motion of the intestine.

21. Guinea pig, weight 490 grams.

This experiment was commenced on the 13th of December, 1912, by injecting 1 c.c. of a solution of colloidal silica in the subcutaneous tissue.

The guinea pig seemed not to show any effect of the treatment, but it died in the morning of the 2nd of January, after 20 days and following the 7th injection. The weight on the 30th day of December had decreased to 440 grams.

Autopsy. Slight edema at the point of injection; absence of fibrinous exudate; muscles pallid, subcutaneous well preserved.

Throughout the tract of the small intestine and the colon hemorrhagic spots, which were also observed on the abdominal face of the diaphragm.

Heart, lungs and spleen normal; blood normally coagulated; liver congested.

Kidneys flaccid, suprarenal capsules hyperemic.

The mucosa of the intestine and of the stomach presented here and there a zone with punctiform hemorrhage.

Meninges somewhat injected; brain slightly hyperemic; marrow of the long bones of the type of the red bone marrow.

22. Guinea pig, weight 540 grams.

Was subjected to experiment the 7th day of January, 1913, by injecting on alternate days, 2 c.c. of a solution of colloidal silica.

Nothing abnormal was observed, except a slight indisposition and, on the days preceding death, a notable prostration.

Death occurred on March 18th, in the morning.
Duration of the experiment, 70 days.
Number of injections, 33.
Table of weights:

January 22, 1913, 525 grams.
February 7, 1913, 460 grams.
February 26, 1913, 440 grams.
March 7, 1913, 350 grams.
March 18, 1913, 280 grams.

Autopsy (made immediately after death.) Organized exudate at the point of injection; subcutaneous connective tissue thin, rather dry; muscles flaccid; heart flaccid; empty; lungs, spleen, kidneys and suprarenal capsules normal; liver congested; gall bladder full, much distended; serosa opaque rather rough.

Intestinal tract injected; mucosa of the small intestine and above all of the duodenum, intensely hyperemic and scattered with hemorrhagic specks.

Stomach with normal walls, with venous injection and with a hyperemic zone in the mucosa.

Meninges injected; cortical substance of the brain hyperemic; marrow of the long bones brownish red.

Examination of the blood put in evidence numerous corpuscles with basophile granulation; corpuscles in vacuole degeneration; some bodies of Cabot and a light increase of eosinophiles (17%).

23. Rabbit, weight 1,800 grams.

Subjected to experiment the 7th day of January, 1913, by injecting 2 c.c. of a solution of colloidal silica on alternate days.

The rabbit at the sixth injection (January 17th) commenced to present an abundant epidermic desquamation, accompanied by a general falling of the hair, which was not slow to be localized on the sides of the abdomen, on the back and inner side of the legs in the form of rounded spots. The skin which remained to view was clear and plainly reddened.

Nothing further of note was observed throughout the whole duration of the experiment, which came to an end on the 28th day of April, when death occurred.

Duration of the experiment, 112 days.

Number of injections, 49.

Table of weights:

January 22, 1913, 1,860 grams.
February 7, 1913, 1,800 grams.
February 26, 1913, 1,800 grams.
March 7, 1913, 1,710 grams.
March 26, 1913, 1,730 grams.
April 22, 1913, 1,640 grams.
April 28, 1913, 1,590 grams.

Autopsy. Notable emaciation; symmetrical hairless spots on the sides of the abdomen and on the back. The inner sides of the legs completely nude with hyperemic skin.

Organized exudate at the point of injection; subcutaneous connective very thin; muscles flaccid, opaque, dry; all of the tissues and viscera dry; absence of liquid in the serosa, which resembled parchment.

Heart, lungs, spleen normal; liver somewhat congested; kidneys hyperemic; suprarenal capsules with hyperemia of the cortex. Intestinal tract injected and full of a greenish frothy liquid. The mucosa of the duodenum, the small inestine and of the large intestine hyperemic with a hemorrhagic zone.

Stomach empty with flaccid walls, thin, which contrasted with the very thick pyloric portion. Mucosa with punctiform hemorrhage both recent and old.

Meninges injected; cerebral substance somewhat hyperemic; marrow of the long bones raspberry red.

Peritoneal Injection of Colloidal Silica and Alimentation With Corn Meal and Herbs.

24. Guinea pig, weight 445 grams.

Subjected to experiment the 13th day of December, 1912, by injecting, on alternate days, 1 c.c. of a solution of colloidal silica.

During life nothing worthy of note came to our attention except an abundant falling of hair.

The guinea pig died on the morning of the 14th of April, 1913.

Duration of the experiment, 122 days.

Number of injections, 52.

Table of weights:

December 30, 1912	390 grams.
January 8, 1913	380 grams.
January 22, 1913	410 grams.
February 7, 1913	380 grams.
February 26, 1913	330 grams.
March 7, 1913	330 grams.
March 26, 1913	330 grams.
April 8, 1913	310 grams.
April 14, 1913	295 grams.

Autopsy. (Made immediately after death). Skin adherent to the subcutaneous connective tissue; tissues extraordinarily dry; muscles pale, flaccid.

Some adherence between the viscera and abdominal walls, by a dense stratum of fibrin. In the left flank between the skin and the wall of the abdomen a nodule of the size of a hazel but containing a caseous substance. Heart empty, flaccid; lungs, spleen, liver, kidneys and suprarenal capsules normal; pericardium and peritoneum without the least quantity of liquid.

Intestinal tract dry, opaque, injected; intestinal mucosa hyperemic internally, also the gastric mucosa, with a hemorrhagic zone. Meninges injected; cortical substance of the brain strongly hyperemic; marrow of the long bones dark red.

25. Guinea pig, weight 330 grams.

The animal was given, on alternate days, injections of 1 c.c. of a solution of colloidal silica.

The experiment was commenced on the 13th of December. At the third injection, by a brusque movement of the animal, the intestine was perforated, which caused its death in the night.

Autopsy. Slight fibrinous exudate scattered here and there throughout the intestinal tract, more abundant and thick at the site of the lesion.

26. Rabbit, weight 1,650 grams.

Injected, on alternate days, 2 c.c. of a solution of colloidal silica.

The experiment was commenced on the 13th day of December, 1912.

The animal remained apparently well for a long time. Only on the first of May we commenced to note symmetrical hairless spots on the sides of the neck, the abdomen and the front and hind limbs. These here and there were so accentuated as to expose the reddened skin, clear and thin. At this time the animal showed an incoordination in walking. The forelegs were held out straight ahead and rigid. This condition steadily became worse and on the first of June there was an evident paretic-spastic walk. At this point, loss of appetite commenced, which continually grew worse; the hair became dry and harsh; the eyes were clear with an appearance of suffering; there was a notable emaciation.

The animal died on the 23rd day of July in the morning.

Duration of the experiment, 214 days.

Total of the injections, 107.

Table of weights:

December	30,	1912,	1,680 grams.
January	8,	1913,	1,630 grams.
January	22,	1913,	1,590 grams.
February	7,	1913,	1,520 grams.
February	26,	1913,	1,620 grams.
March	26,	1913,	1,650 grams.
April	22,	1913,	1,650 grams.
May	21,	1913,	1,560 grams.
June	11,	1913,	1,450 grams.
July	2,	1913,	1,410 grams.

July 23, 1913, 1,200 grams.

Autopsy. (Made immediately after death). Besides the cutaneous lesions described above, a marked anemia.

The muscles and all the internal organs were excessively pale; extreme dryness of the tissues and of the serosa, which appeared opaque, harsh and adherent.

Heart, lungs, liver and spleen pale but normal.

Kidneys flaccid and on cutting appeared rather lardaceous; nothing of note in the suprarenal capsules.

The intestinal tract thin, very transparent and in the mucosa numerous specks and an extensive hemorrhagic zone.

Walls of the stomach thinned to the veil of an onion except the pyloric portion which presented a thickening so great as to have on cutting a thickness of about one centimeter.

Meninges injected; the surface of the cerebral cortex hyperemic, and rather readily friable.

Marrow of the long bones intense brownish red.

An examination of the blood disclosed numerous corpuscles with basophile granulation.

RECAPITULATION.

In this series of experiments the same progress of the intoxication was established as in the preceding series, and that maize alimentation does not produce a notable modification, except a considerable retardation in the manifestation of the toxic effects.

Only one guinea pig died after seven injections; the other animals instead lived several days and one rabbit survived to the 214th day, having received 107 peritoneal injections.

The symptomatology of the intoxications was the same. They were as follows: Decline, loss of appetite, falling of hair in spots, spastic paresis, and at the autopsy, besides the cutaneous lesions, there was observed hemorrhage in spots in the stomach and the intestine, thinness of the walls of the same, hepatic congestion, usually a fullness of the gall bladder, a hyperemia of the meninges and of the cortical substance of the brain.

Also the marrow of the long bones presented a reddish brown color more or less intense, and an examination of the blood, made in only a few cases, showed numerous corpuscles with basophile granulation.

Ingestion of a Solution of Colloidal Silica and Ordinary Alimentation.

The results of the experiments, heretofore set out, demonstrate clearly on the one hand the toxic action of silica, injected under the skin or into the peritoneum, but on the other hand they do not demonstrate that the same toxic action would follow the administration of colloidal silica by the mouth. Heretofore it has always been supposed that it was not possible to be absorbed by this route, that coagulated and aggregated it passed unaltered through the stomach and the intestine. To complete the experiment was of vital interest to us, for if pellagra were contracted with potable water, the etiological agent, which according to us is the silica dissolved in it, ought to be absorbed by the gastro-intestinal route.

To this end we have subjected a monkey to experiment, in that he was made to drink, instead of common water, a solution of colloidal silica prepared by diluting 100 c.c. of the solution used for injections in one liter of distilled water. Therefore the monkey drank a water containing 0.7114 grams of SiO_2 per liter. It was not possible to use a solution more concentrate or still worse the solution of silica without dilution, because this, having scarcely reached the mouth, coagulates and becomes very disgusting so that the monkey would not drink at all.

27. Monkey (*Cynocephalus papio*) young male of about two years.

The animal arrived at the institute the 1st of January, 1913. He was kept some time in quiet, furnished good food, consisting of biscuit, potato, honey, milk, bread and leaves of cabbage and lettuce and given to drink the water of the Institute (Marcia).

On the 9th of January the experiment was commenced substituting for the common water the dilution of colloidal silica.

Up to the 29th of March the monkey remained in the best of humor and had a good appetite. From that day he commenced to become wretched; remained voluntarily backed up in the most obscure angle of the cage and was not lively and cheerful. Confinement was ill supported; during the night was seized by an access of fury, broke the metallic bars of the back and lower part of the cage, cutting them with his teeth.

There was noted a certain pallor of the ears, of the buccal mucosa and of the skin around the eyes.

There was depilation of the breast and of the inner side of the forearm.

The depilation increased from day to day and the spots on the breast and the forearm extended to the neck. On the 22nd of April observed an intense erythema of the callosity, especially on the left side.

The vesicles which were first observed, numerous and isolate, one after the other gradually became confluent and formed extensive blisters of circular form, one of which on the left side attained the size of a ten centime coin. The liquid contained in it was serous.

The monkey at this time appeared depressed and ate fastidiously.

Observed closely, there was noted a crust concealed by the hair in the dorso-lumbar region. The breast, the arms and the neck were quite hairless.

On the 2nd day of May, the breast, along the median line, presented an extensive erythematous zone of irregular form.

At this time the blisters broke, the sores underneath for a few days discharged a sero-sanguinous liquid. They formed large scabs which later fell off leaving the skin thin, clear, with a mother of pearl reflection. The falling of the hair ceased on the trunk and arms and from the hairless spots the skin peeled off in thin clear scales. On the contrary the tail became denuded so that by the 2nd of June it was completely bare with an extensive zone covered with vesicles and blisters with here and there an open sore.

During the night the monkey had diarrhoea which continued until the 10th of June. During this period there was greater prostration, accompanied by somnolence and a slight generalized tremor.

Nothing better or worse was noted in the general conditions until the first of the month of September. Instead the local conditions were much improved, so much so that except the hairless zones on the arm, the breast, the neck, which remained, the callosity and the tail almost completely healed and were again covered with a discrete amount of thin light hair.

In the middle of September the prostration and emaciation were accentuated and the monkey remained almost always motionless in a corner of the cage with the head inclined.

There was a notable hyperesthesia. To come into the room, to make the least noise, to clap the hands, were sufficient to give him a start.

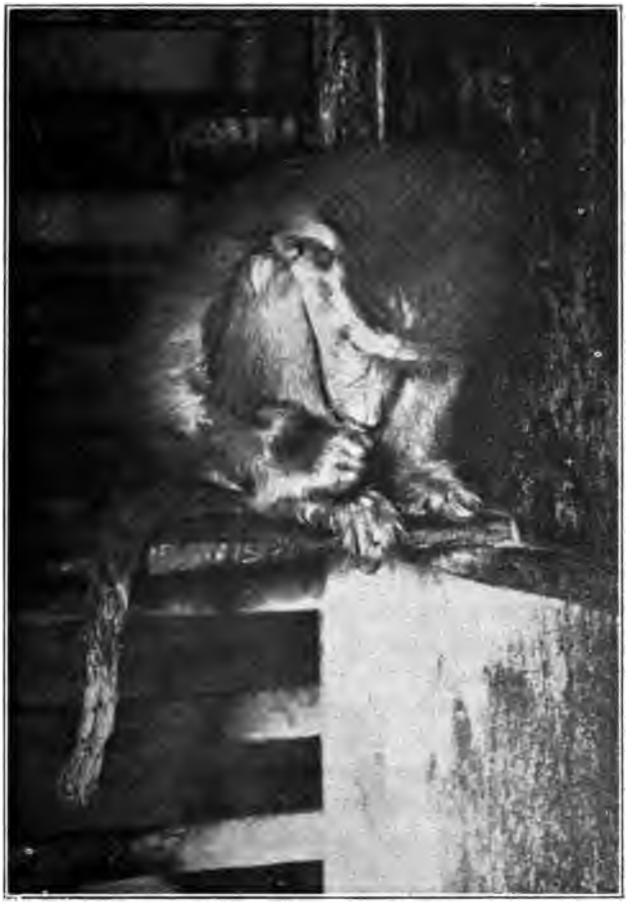
At this time the cutaneous phenomena were observed to be accentuated anew and by the first of October the buttocks had become intensely red; vesicles formed anew on the tail which became sore and the falling of the hair was notable on the top of the feet where the skin showed an evident erythema.

The hyperesthesia and emaciation increased from day to day with a contemporaneous increase of prostration. The animal remained almost all day doubled upon himself with his nose between his legs which were flexed upon the chest (Fig. 2).

On the 20th of November he was noted to walk almost dragging the hind limbs, aided much by the arms.

He remained almost constantly with his head between his legs, for the most part motionless. The tremors increased and with them the hyperesthesia; the least improvised noise was sufficient to give him a start.

On the 10th of December noted that the skin of the but-



(Fig. 2.)

tocks was cracked in longtitudinal stria which ran through the callosity in its whole length.

The monkey remained almost all the time squatted in the most obscure part of the cage with the legs held flexed between the body and the arms. The head hung between the knees. The eyes were weak but full and clear. He walked but rarely and with great effort. Was very prostrated and ate very little.

On the 20th of December noted a certain dispnea and if touched on the abdomen he cried out sharply. Has lost all his vivacity.

On the 8th day of January observed an increase of the trembling of the forelimbs, also that the lower limbs were held in flexion. Voluntary motion was considerably reduced, no longer took food with his hands and refused the sugar of which he was very fond.

Noted a resistance to passive movement, were not able to make complete passive extension of the limbs; during these attempts it was seen that the hands especially were constantly in flexion and agitated by severe tremors. The tendinous reflexes were exaggerated in both the upper and lower limbs. The condition of hyperesthesia was notable; to touch lightly on the breast or the belly was sufficient to cause the monkey to cry out with pain.

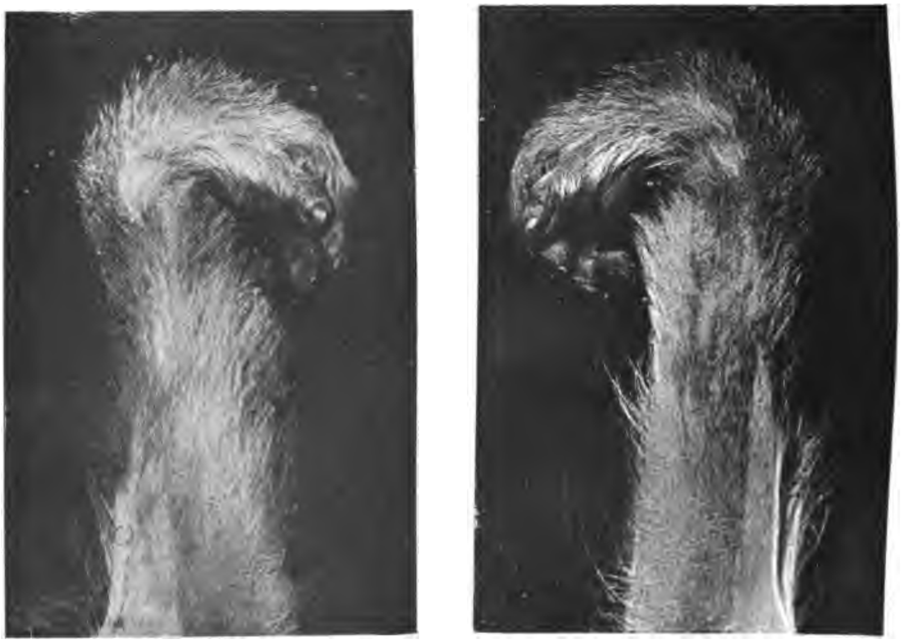


Fig. 3.

The trophic disturbances increased, the hair fell from large spots and the skin, where it was atrophic, was wrinkled in hard folds.

January 13. The spastic paresis became more notable; the animal was no longer nourished, since it was no longer able to convey the food to its mouth. It did not move from its position in the most obscure corner of the cage. It was weak from diarrhoea.

The morning of the 14th found the monkey in a pitiful state; he was dispneic; all four limbs were in spastic contraction (figures 3 and 4) and a continuous tremor agitated the whole body. Attempted to eat but was absolutely unable to take food with the hand. It was necessary to feed him, but even the muscles of mastication had lost their strength; food was placed in the buccal pocket and later returned intact without being able to masticate.

On the 6th, after an attack of convulsions, he lay pros-

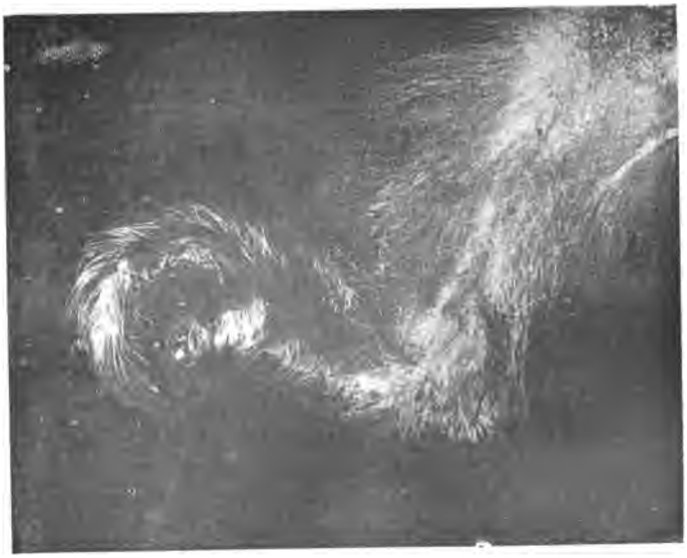
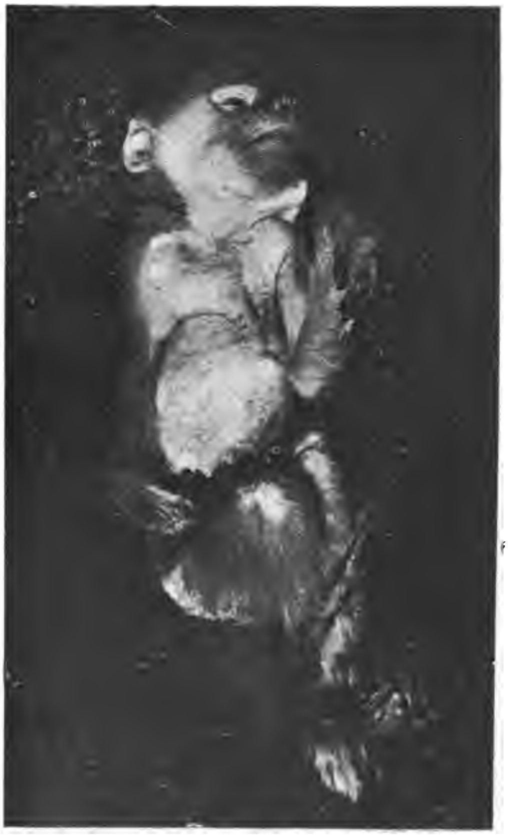


Fig. 4.

trate on the bottom of the cage in spastic contraction, entirely bent upon himself, agitated by violent tremors. The dispnea was increased; here was involuntary discharge of diarrhoeic feces.

Called, he turned his weakly weeping eyes, and at the sight of food showed that he desired to have it, but when it was placed near his mouth he was not able to take it. His condition was continually and very rapidly aggravated until the cessation of the tremors and the cries indicated that his death

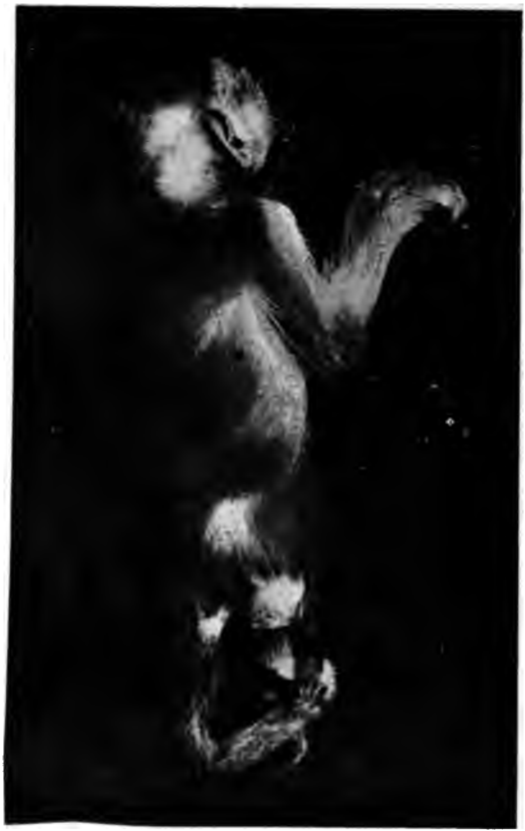


(Fig. 5.)

had occurred after a year and five days from the beginning of the experiment.

Autopsy. Cadaver emaciated. Skin deprived of all connection with the subcutaneous connective tissue, hairless on various parts of the body. The chest in fact, the abdomen, the cheeks, the sides of the neck, the inner sides of both the fore and hind limbs, the elbow, the knee, the upper metacarpal region, the phalanges of the lower limbs and the lower half of the tail were completely denuded (Fig. 5 and 6).

On the outside skin, numerous thin clear epidermic scales.



(Fig. 6.)

The skin of the callosity presented a red base for white streaks of subepidermic cicatrix. Panniculus adiposus thin; muscles pale, flaccid, atropied. No peritoneal or pleural liquid. Pericardial liquid scarce, limpid, colorless. Heart flaccid, myocardium of a dark color. Blood fluid slightly coagulable; lungs normal; thyroid and thymus normal; liver somewhat congested, normal as to size and consistency; gall bladder full, turgid; kidneys pallid, little distinction between the two substances. Suprarenal capsules somewhat thickened with hyperemic cortex. Spleen and pancreas normal.

Stomach full of food with walls so thin that it was easy to see the contents (Fig. 7). Intestinal tract full of greenish frothy liquid, with walls pale, thin and transparent which revealed a notable venous injection. Along the small intestine, at two points, a short distance from each other, two contractions were noted.

Serosa of the duodenum hyperemic. Hyperemia in spots throughout the serosa of the large intestine and the rectum. Contents of the stomach dry, compact, covered with a dense stratum of whitish mucus.

Mucosa of the stomach congested, in some places hemorrhagic. Mucosa of the duodenum congested with numerous hemorrhagic spots which also extended to the small intestine, the colon and the rectum.

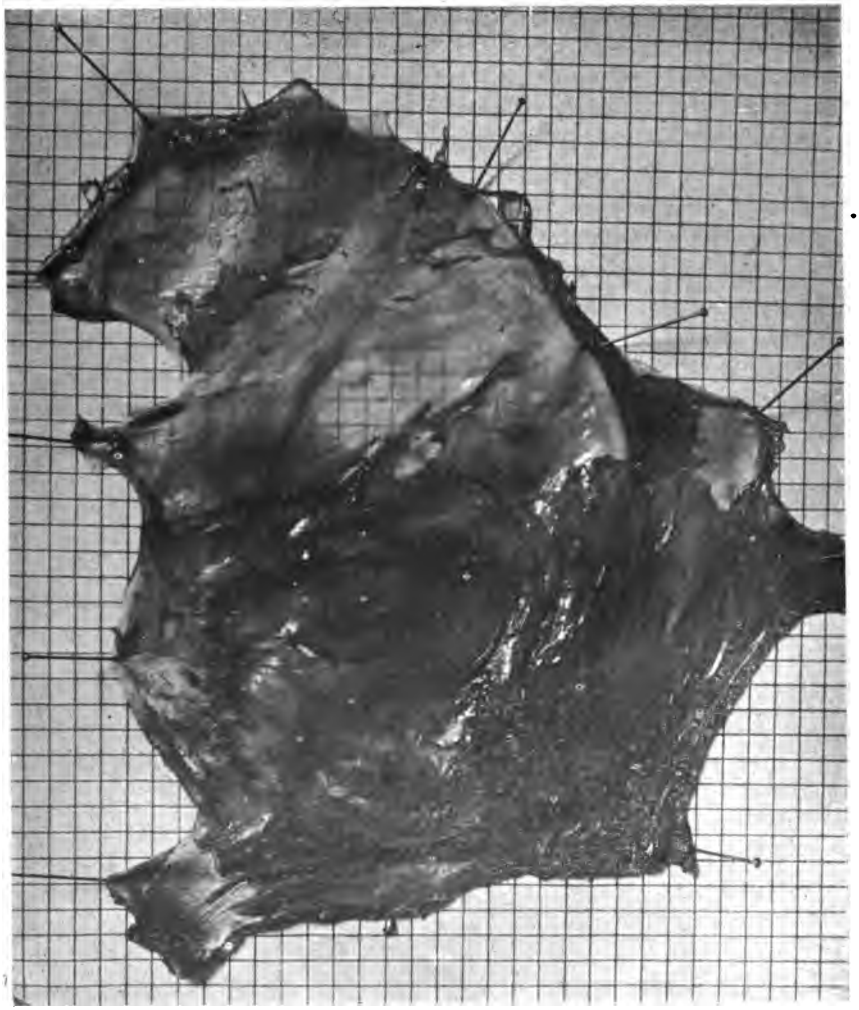
The dura mater on inspection opaque with some adherence to the cranial walls. Pia mater hyperemic. Cerebral cortex diffusely hyperemic; cerebral substance soft, easily broken.

Marrow of the long bones brownish red.

Bacteriological examination of the blood, taken from the heart, entirely negative.

RECAPITULATION.

This experiment demontsrates evidently that the colloidal silica, administered by the mouth in small quantity, is diffused and accumulates in the organism, producing the same pernicious effects which we noted in the animals in which the



(Fig. 7.)

colloidal silica was injected under the skin or the peritoneum.

Injection Into the Peritoneum of a Suspension of Gelatinous Silica in Distilled Water and Alimentation With Bran and Herbs.

Not content to have established the noxious action of a solution of colloidal silica either by subcutaneous and intraperitoneal injection, or by the mouth, we decided to extend our experiments to gelatinous silica, which is in a state of aggregation much more dense to be absorbed readily throughout the organism and to produce intoxication.

The suspension of gelatinous silica was made by triturating 1 gm. of the gelatin in a porcelain mortar and diluting with 100 c.c. of distilled water.

The gelatinous silica contained 96.06% of water; therefore, the quantity of the oxid of silicon in 100 c.c. of water was 0.0394.

28. Guinea pig, weight 400 grams.

Commenced the experiment the 16th of December by injecting in the peritoneum, on alternate days, 1 c.c. of a suspension of gelatinous silica.

The guinea pig presented nothing abnormal during the early period of the experiment; later he showed weakness and insufficient nourishment without further notable symptoms. Died the 5th of February in the morning.

Duration of the experiment, 51 days.

Injections, 22.

Table of weights:

December	30,	1912,	380 grams.
January	8,	1913,	340 grams.
January	22,	1913,	320 grams.
February	5,	1913,	250 grams.

Autopsy. (Made immediately after death). Subcutaneous connective thin; muscles pallid and flaccid. The abdominal wall adhered to the abdominal tract by means of a thin, stringy viscid layer. There was also adherence throughout the intestinal tract, between it and the stomach and between it and the spleen.

There was no pleural pericardial or peritoneal fluid.

Heart flaccid, blood not well coagulated; lungs with some nodules of congestion; liver congested; spleen normal; kidneys and suprarenal capsules hyperemic.

Small intestine injected, distended with a greenish, frothy liquid. Throughout the mucosa, a zone with punctiform hemorrhage.

Stomach empty, adhered to the great omentum, from which it could still be easily separated; mucosa congested; in the cardiac region, an extravasation of blood and here and there submucous hemorrhage.

Injection and hyperemia of the vessels of the meninges and the brain.

Marrow of the long bones brownish red.

29. Guinea pig, weight 350 grams.

Injected on alternate days, 1 c.c. of gelatinous silica in suspension.

Made the first injection on the 19th of November, 1912. Without apparent symptoms, the guinea pig died after the fourth injection, on the 29th day of November.

Duration of the experiment, 10 days.

Injections, 4.

Weight at the moment of death, 330 grams.

Autopsy. Nothing in the connective tissue; subcutaneous gelatinous edema in correspondence with the point of injection on the left side, with exudate apparently fibrous and stringy on all the muscular wall in correspondence with the exudate.

Peritoneal liquid sero-hemorrhagic.

Heart, lungs, spleen normal; liver congested; kidneys hyperemic; suprarenal capsules intensely hyperemic.

Intestine, red with some deposit of fibrin; mucosa hyperemic especially in the small intestine.

Stomach empty with the walls flaccid and the mucosa normal.

Meninges hyperemic; cortical substance of the brain hyperemic; marrow of the long bones brownish red.

Bacteriological examination of the blood taken from the heart negative.

30. Guinea pig, weight 400 grams.

Commenced the experiment on the 30th day of November, treating the guinea pig the same as the preceding. Also this one, without appreciable symptoms, died after a short time, its weight having decreased on the day of death (December 14) to 330 grams.

Duration of the experiment, 15 days.

Injections, 6.

Autopsy. Organized exudate at the point of injection, especially on the left. Liquid sero-hemorrhagic, fibrinous in the peritoneum and coagula of fibrin throughout the intestinal tract and the viscera; adherence between the parietal and visceral peritoneum.

Heart flaccid; spleen normal; lungs normal; liver somewhat congested; gall bladder full and distended; kidneys with the cortical substance hyperemic; suprarenal capsules with punctiform hemorrhage.

Hemorrhage in spots throughout the intestinal tract, especially in the duodenum and small intestine; none in the colon. Mucosa of the duodenum and the small intestine intensely hyperemic with hemorrhage in spots.

Stomach empty, without appreciable alterations.

Meninges intensely hyperemic; cortical substance of the brain hyperemic, congested and here and there punctiform hemorrhage; marrow of the long bones brownish red.

Nothing in the bacteriological examination of the blood and the exudates.

31. Rabbit, weight 1,970 grams.

Commenced the experiment on the 19th of November, injecting in the peritoneum, on alternate days, 2 c.c. of the solution of silica.

After eight injections, on the 9th day of December, it was noted that the animal walked with difficulty; it was slow in its movements and it was necessary to arouse it to movement, at this time it refused food and seemed to be declining. This state of prostration continued for about ten days, then followed a gradual improvement, the appetite, returned and by the 26th of December all sickness had disappeared.

Subsequently everything returned to the normal and except a progressive emaciation, there was nothing notable until the end of April. Then the hair commenced to fall abundantly from the flanks, the back and the neck, and formed large hairless spots which were plainly visible with distinct edges by the end of May. The skin scaled off abundantly and there was at the same time a rapid and visible decline; the appetite declined, on the following days before the 15th of June it had no nourishment except a very little of herbs. On the 16th of June on being taken from its cage to study its movements, it was noted that there was an involuntary emission of urine.

In this condition it survived until the 2nd of July, on which day the animal died.

Duration of the experiment, 226 days.

Number of injections, 95.

Table of weights:

November	28,	1912,	1,930 grams.
December	11,	1912,	1,840 grams.
December	30,	1912,	1,960 grams.
January	8,	1913,	1,900 grams.
January,	22,	1913,	1,930 grams.
February	7,	1913,	1,930 grams.
February	26,	1913,	1,860 grams.
March	26,	1913,	1,870 grams.
April	22,	1913,	1,800 grams.
May	10,	1913,	1,730 grams.
May	26,	1913,	1,610 grams.
June	11,	1913,	1,500 grams.
June	27,	1913,	1,380 grams.
July	2,	1913,	1,250 grams.

Autopsy. Extensive hairless spots on the back, the flanks and the neck; very great emaciation; muscles pale, flaccid, dry, adherent.

The intestinal tract and serosa dry like parchment; little and frail adherence between the intestinal tract and the walls of the abdomen.

Lungs normal; heart flaccid; spleen, liver normal; kidneys and suprarenal capsules hyperemic.

Venous injection of the intestinal tract with some hemorrhage in the serosa. The mucosa was covered with a vast hemorrhagic zone, as much in the small intestine as in the duodenum.

The stomach with a portion of the greater curvature so thin as to disclose its small amount of contents; the pyloric portion was hard and very rough. Throughout the mucosa, an extensive congested zone with hemorrhages, some old and others very recent.

Meninges hyperemic; cortical substance of the brain and of the medulla intensely hyperemic; marrow of the long bones brownish red.

RECAPITULATION.

The injections with a suspension of gelatinous silica and alimentation of the animals with bran and herbs have produced the same effects as the injections of a solution of colloidal silica. It is not possible to distinguish a modification of the duration of the action, for while in two cases (No. 29 and 30) death occurred in a very short time, in the other two (No. 28 and 31) the duration of the experiment was very much protracted, and the rabbit No. 31 survived 226 days with 95 injections.

There were noted also the same disturbances and the same anatomical alterations as were found in the animals of the preceding series.

Therefore, there is no doubt of the absorption of the silica in the gelatinous condition, by peritoneal injection.

Injections Into the Peritoneum of a Suspension of Gelatinous Silica and Alimentation With Corn Meal and Herbs.

In this series of experiments we desired to establish the influence of maize alimentation upon the intoxication with gelatinous silica, as we did with colloidal silica.

32. Guinea pig, weight 470 grams.

Experiment initiated the 13th of December by injecting, on alternate days, 1 c.c. of a suspension of gelatinous silica.

The guinea pig except an abundant *defluvium* of hair which commenced at once after the first injections did not present anything abnormal until the day of death which occurred on the morning of the 28th day of January.

Duration of the experiment, 46 days.

Number of injections, 20.

Table of weights:

January 2, 1913, 460 grams.
January 22, 1913, 410 grams.
January 28, 1913, 395 grams.

Autopsy. (Made immediately after death). Falling of hair localized in preference on the ventral side, which appeared almost nude.

Notable emaciation; muscles pale, flaccid; fibrinous deposit on the whole intestinal tract and the internal organs.

Heart and lungs normal; absence of pleural, pericardial and peritoneal liquid. Serosa opaque and dry; liver slightly congested; gall bladder full, distended; spleen normal; kidneys flaccid without distinction between their two substances; suprarenal capsules with hyperemia of the cortex; urinary bladder full.

Hemorrhage throughout the intestinal tract, of which the mucosa, especially of the duodenum, jejunum and ileum was congested with punctiform hemorrhage scattered here and there.

Stomach empty, flaccid, with the mucosa intensely and diffusely hyperemic, and in a certain point clearly congested; marrow of the long bones dark raspberry red; meninges and cerebral substance hyperemic.

33. Rabbit, weight 1,850 grams.

Commenced the experiment the 13th of December, 1912, injecting on alternate days, 2 c.c. of a suspension of gelatinous silica.

The rabbit, without apparently showing any disturbance lost flesh very notably. On the first of February, observed an abundant falling of the hair which was not slow and localized on the sides of the body and soon extended to the back, to the inner side of the limbs and principally to the base of the tail. At the same time the weight was much diminished and the hairless spots scaled off in large flakes.

The animal lost its appetite and by the 20th of April almost entirely refused food. On the 24th of April noted that there was a slight paresis of the hind quarters, so that they were dragged in walking.

The rabbit became worse from day to day; on the 27th of April recognized a complete paralysis of the hind quarters; it was no longer able to move and we were constrained to place its food under its nose so that it could eat, but it refused entirely. It died the 6th of May in the morning.

Duration of the experiment, 145 days.

Number of injections, 61.

Table of weights:

December	30,	1912,	1,830 grams.
January	8,	1913,	1,830 grams.
January	22,	1913,	1,760 grams.
February	7,	1913,	1,580 grams.
February	26,	1913,	1,590 grams.
March	7,	1913,	1,480 grams.
March	26,	1913,	1,440 grams.
April	10,	1913,	1,450 grams.
April	22,	1913,	1,490 grams.
May	6,	1913,	1,180 grams.

Autopsy. (Made immediately after death). On all the back, the flanks and the inner side of the limbs hairless spots and the skin intensely hyperemic. The tail completely bare, of a bright red color with an ulcerated zone. Muscles flaccid, pale, opaque, stuck together; all the tissues dry and the serosa hard like parchment.

A rather thin fibrous deposit throughout the tract of the intestine and the internal organs; spleen, kidneys, suprarenal capsules normal; liver slightly congested; heart pale, very flaccid. The intestine moniliform, with zones very dilated and walls thin, which by their transparency exposed to view a frothy greenish liquid, alternating with zones much contracted and the walls thick. (Fig. 8.) Numerous hemorrhagic spots in the mucosa and venous injection in the internal serosa. The stomach with walls so thin that the substance contained in it showed through; on the other hand the pyloric portion was thick and hard. Here the wall of the stomach was about 1 centimeter thick. Duodenum dilated like an ampule with walls thin, transparent; throughout the mucosa hemorrhagic spots were noted. Meninges injected, cortical substance of the brain intensely hyperemic; marrow of the long bones brownish red.

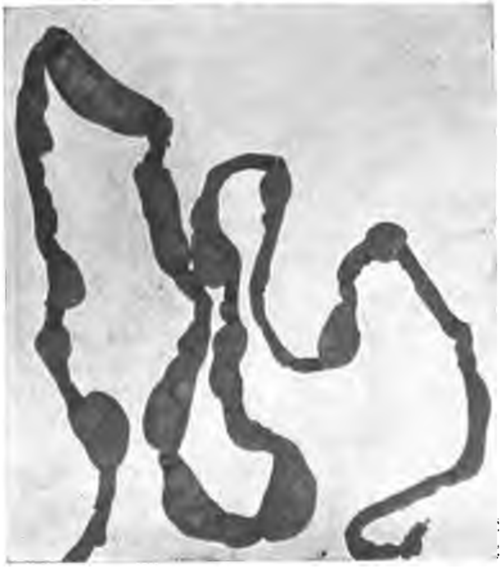


Fig. 8.

RECAPITULATION.

In the two animals subjected to this experiment, death occurred after a period relatively long, since the guinea pig lived 46 days and the rabbit 145.

As in the other experiments, the rabbit had more resistance to the injections than the guinea pig, but it also presented a picture more grave and more complete. In every case, the change of alimentation has produced no modification of the symptomatology of the intoxication, nor modifications of the conditions recognized in the necroscopic findings. Like all the alterations described before they were ascribed to the skin, the digestive tract and the nervous system.

Therefore we are able to state that alimentation with maize has no influence upon the intoxication of the animal with a suspension of gelatinous silica.

Ingestion of Silica in the Gelatinous State and Alimentation With Bran and Herbs.

In this series of experiments there was given to the animals to eat the sole ration of bran in which was accurately mixed the quantity of 5 grams of gelatinous silica first triturated and suspended in a little water. Therefore the animals daily ate a quantity of oxid of silicon of 0.197 grams, the gelatinous silica containing as we have already stated, 96.06% of water.

34. Guinea pig, weight 450 grams.

Initiated the experiment the 26th of November, 1912.

The animal except a state of prostration occurring in the last eight days of life accompanied by a discrete loss of appetite, presented nothing of note.

On the 5th of February, 1913, it was found dead in the cage.

Duration of the experiment, 72 days.

Table of weights:

November 28, 1912, 480 grams.
December 11, 1912, 480 grams.
December 30, 1912, 435 grams.

January 8, 1913,	420 grams.
January 22, 1913,	380 grams.
February 5, 1913,	320 grams.

Autopsy. Subcutaneous tissues thin; abdominal walls normal; muscles somewhat pale.

Heart, lungs, spleen normal; liver congested. Small intestine and colon hyperemic; intense hyperemia of the intestinal mucosa.

Stomach full of food with walls somewhat thin; mucosa hyperemic.

Kidneys hyperemic with slight distinction between the two substances; suprarenal capsules slightly hyperemic.

Cerebral vessels injected and diffuse hyperemia of the cortical substance; cerebral and spinal meninges injected; marrow of the long bones brownish red.

35. Guinea pig, weight 480 grams.

Commenced the experiment on the 20th day of February, 1913.

Nothing notable was observed during the whole time of the experiment which lasted until the 15th of May, the day on which the animal succumbed.

Only three days before death there was recognized a notable prostration accompanied by a complete loss of appetite.

Duration of the experiment, 84 days.

Table of weights:

March 10, 1913,	480 grams.
March 26, 1913,	460 grams.
April 12, 1913,	500 grams.
April 22, 1913,	440 grams.
May 10, 1913,	400 grams.
May 15, 1913,	330 grams.

Autopsy. Subcutaneous tissue normal, abdominal walls normal, muscles pale, rather dry.

Heart flaccid, blood pale, fluid; lungs, pleura normal; liver congested; spleen, kidneys, suprarenal capsules normal.

The intestinal tract injected; duodenum and small intestine with the mucosa hyperemic and a zone of punctiform hemorrhage.

Stomach full with the walls very thin, transparent; the food contained in it was compact, dry, covered with a dense stratum of white opaque mucus. The mucosa somewhat congested with here and there hemorrhagic spots.

Cerebral and spinal meninges hyperemic; intense hyperemia of the surface of the brain and the spinal cord.

Marrow of the long bones dark red.

36. Rabbit, weight 1,600 grams.

The experiment was commenced the 26th of November, 1912.

The animal in appearance seemed but little to resent the special treatment, but grew and increased in weight.

In the beginning of January there was manifest a *defluvium* of hair over the whole body, a defluvium which was accentuated and localized especially on the sides of the abdomen and on the inner sides of the thighs. On the 7th of February hairless spots were distinctly observed in these regions and it was noted that the skin, on the zone uncovered, scaled off abundantly. The appetite and vivacity remained normal until almost the day of death which happened on the morning of the 28th of May, 1913, and only 24 hours before did it refuse to take food.

Duration of the experiment, 184 days.

Table of weights:

November	28,	1912,	1,650 grams.
December	11,	1912,	1,680 grams.
December	30,	1912,	1,600 grams.
January	8,	1913,	1,600 grams.
January	22,	1913,	1,650 grams.
February	7,	1913,	1,740 grams.
February	26,	1913,	1,750 grams.
March	10,	1913,	1,730 grams.
March	26,	1913,	1,770 grams.
April	12,	1913,	1,730 grams.

April 22, 1913, 1,770 grams.
May 10, 1913, 1,720 grams.
May 28, 1913, 1,700 grams.

Autopsy. (Made immediately after death). Two long hairless spots, symmetrical on the sides of the abdomen and complete depilation of the internal face of the thighs and the axillae.

Panniculus adiposus normal, muscles rather pale; abdominal walls normal.

Heart flaccid, and the pericardium normal; lungs, spleen, kidneys, suprarenal capsules normal.

Tract of the intestine injected and the mucosa of the small intestine hyperemic, with a zone intensely congested and here and there punctiform hemorrhage; secum and rectum distended and full of a great quantity of feces.

Stomach full of food not digested; walls rather thin and gastric mucosa intensely congested, with hemorrhagic zone; liver slightly congested.

Cerebral and spinal meninges somewhat injected; superficial vessels of the encephalon and medulla hyperemic.

Marrow of the long bones brownish red.

37. Rabbit, weight 1,950 grams.

The experiment was commenced the 20th of February.

During the whole course of the experiment, which was protracted until the 12th of May, nothing was observed of note except an exaggerated *defluvium* of hair generalized over the whole body and a certain grade of prostration during the last days of life.

Duration of the experiment, 82 days.

Table of weights:

March 10, 1913, 1,980 grams.
March 26, 1913, 1,930 grams.
April 12, 1913, 1,930 grams.
April 22, 1913, 1,860 grams.
May 10, 1913, 1,820 grams.
May 12, 1913, 1,730 grams.

Autopsy. (Made at once after death). Hair opaque, thin, harsh; subcutaneous tissue thin; muscles dry, pale; abdominal walls dry and sticky.

Peritoneum, pericardium, dry, opaque, adherent.

Heart flaccid, full of pale liquid blood.

Lungs and spleen normal; liver congested.

Intestinal tract slightly injected, opaque, very dry.

Mucosa of the duodenum and small intestine with a hyperemic zone and numerous hemorrhagic spots.

Stomach full of food with the mucosa intensely and uniformly congested. Punctiform hemorrhages both old and very recent.

Kidneys slightly congested, suprarenal capsules normal.

Meninges injected; superficial vessels of the encephalon and spinal cord hyperemic.

Marrow of the long bones dark red.

RECAPITULATION.

With the administration by the mouth, of silica in the gelatinous state we have not been able to observe notable disturbances during life. The cutaneous lesions were found only in the rabbit which resisted so long the action of the silica, and which, contrary to the normal, increased considerably and progressively in weight.

The increase should be considered only apparent, because the experiment was commenced before the animal had attained its maximum of development which it attained notwithstanding the obstacle of the ingestions.

The lesions, found at autopsy, were identical with those found in the animals of former experiments. Among them predominated the alterations ascribed to the digestive canal (hyperemia, hemorrhage, thinning of the walls of the stomach and intestine) and to the nervous system.

With the exception of the rabbit, No. 36, which lived 184 days, the other animals died from the 72nd to the 84th day of the experiment.

Ingestion of Silica in the Gelatinous State and Alimentation With Corn Meal and Herbs.

The animals reecived the same quantity of gelatinous silica as in the last experiment, with the difference that the silica was mixed with corn meal instead of with bran.

38. Guinea pig, weight 400 grams.

The guinea pig was subjected to the experiment the 13th day of December, 1912.

Until the 23rd of December nothing of note. On the morning of the 23rd the guinea pig, after a period of agitation, fell supine, inert. Having remained in this state of immobility for some time (about 20 minutes) little by little it came to itself but remained in extraordinary excitation. Its eyes were terrified and rolling at the least noise. From the state of excitement, during which it bit the iron bars of the cage and cried in a painful manner, it passed into one of depression; laid motionless and seemed unable to control its legs. Nothing was sufficient to agitate it but it fell more into depression which was always preceded by general tremors.

This condition continued more or less intense until the day of death, which occurred the 15th day of February.

Duration of the experiment, 65 days.

Table of weights:

December	30,	1912,	380 grams.
January	8,	1913,	400 grams.
January	22,	1913,	420 grams.
February	7,	1913,	400 grams.
February	15,	1913,	330 grams.

Autopsy. Subcutaneous tissue rather thin; walls of the abdomen normal; muscles pale.

Heart flaccid, pale, empty.

Lungs, liver and spleen normal.

Kidneys somewhat hyperemic; the two substances not well differentiated; suprarenal capsules normal.

Small intestine strongly injected; mucosa with here and there a zone intensely hyperemic, scattered over with hemorrhagic spots; stomach empty with walls very thin and the mucosa much congested.

Marrow of the long bones dark brown.

Cerebral surface hyperemic; meninges injected.

39. Rabbit, weight 1,770 grams.

Commenced the experiment the 13th day of December.

Toward the end of January commenced to note an abundant falling of hair, which was localized along the back, and afterwards in symmetrical spots on the sides of the belly and on the abdomen.

The rabbit did not present either prostration or emaciation; it progressively increased in weight until death, which occurred after four days in which the rabbit did not have a defecation.

Duration of the experiment, 92 days.

Table of weights:

December	30,	1912,	1,770 grams.
January	8,	1913,	1,980 grams.
January	22,	1913,	2,100 grams.
February	7,	1913,	2,120 grams.
February	26,	1913,	2,120 grams.
March	14,	1913,	2,130 grams.

Autopsy. Extensive hairless spots on the back, the flanks and the belly; skin denuded, showing epidermic desquamation more or less extensive.

Subcutaneous tissue conserved, but like the muscles dry and stuck together. Abdominal walls normal; serosa opaque, dry and adherent.

Heart, lungs, spleen, kidneys and suprarenal capsules normal; liver plainly congested.

Intestinal tract strongly injected, enormously distended by gas and by a greenish frothy liquid; rectum and rectal ampule greatly distended by large hard masses; intestinal mucosa sprinkled with a hyperemic zone and punctiform hemorrhage.

Stomach empty of food, greatly distended by gas; in the serosa venous injection and hemorrhagic spots, which also extended into the mucosa; walls thin.

Meninges injected; cortical substance of the brain hyperemic.

Marrow of the long bones dark raspberry red.

40. Guinea pig, weight 390 grams.

Commenced the experiment the 28th of February, 1913.

The guinea pig, if we except a notable emaciation and a discrete falling of hair, died the 15th of April, without having presented anything in life.

Duration of the experiment, 47 days.

Table of weights:

March 10,	1913,	330 grams.
March 26,	1913,	320 grams.
April 8,	1913,	280 grams.
April 15,	1913,	240 grams.

Autopsy. (Made at once after death). Subcutaneous tissue very thin; muscles pale, rather dry; abdominal walls normal; serosa dense and dry.

Heart empty, flaccid; lungs, liver, spleen, kidneys and suprarenal capsules normal; urinary bladder full, enormously distended.

Venous injection the whole length of the intestinal tract. The mucosa of the duodenum and the small intestine scattered with numerous point like hemorrhages and hyperemic spots.

Stomach empty; mucosa intensely congested, brownish red.

Meninges with slight venous injection; cortical substance of the brain slightly hyperemic.

Marrow of the long bones brownish red.

41. Rabbit, weight 2,800 grams.

The experiment was commenced the 17th day of March.

Also this animal, like the others, presented throughout the whole length of the experiment but few facts worthy of note.

The *defluvium* of hair was abundant but uniform; the appetite except a few days of loss of appetite recorded about the middle of May, remained normal. Defecation and urination were normal.

On the first of June the appetite diminished notably and during the three days before death (June 9) the animal refused food entirely.

Duration of the experiment, 85 days.

Table of weights:

March 26, 1913,	2,770 grams.
April 10, 1913,	2,440 grams.
April 25, 1913,	2,400 grams.
May 5, 1913,	2,270 grams.
May 16, 1913,	2,300 grams.
June 2, 1913,	2,260 grams.
June 9, 1913,	2,100 grams.

Autopsy. Subcutaneous tissue thin, muscles pale, flaccid, dry.

Serosa opaque, dry.

Heart flaccid, full of blood not well coagulated.

Lungs, liver, spleen, kidneys and suprarenal capsules normal.

Intestine injected throughout its whole length, full of gas and a frothy greenish liquid, but not uniformly. It was of moniliform aspect. The dilated zones were transparent and the mucosa very hyperemic with numerous punctiform hemorrhages.

Stomach with the walls very thin with the exception of the pyloric portion which presented a thickening as in spastic contraction.

The mucosa was congested and in the greater curvature besides numerous hemorrhagic zones, three small ulcerations were observed with thickened borders.

The meninges were injected and the cortical substance of the brain was hyperemic, especially the frontal and occipital lobes.

Marrow of the long bones brownish red.

RECAPITULATION.

The substitution of corn meal for bran produced no modifications worthy of note in the toxic process described in the former series.

We may only note, in rabbit No. 41, alterations of the skin with manifest and abundant falling of the hair; in guinea pig No. 38, a state of notable agitation and excitation followed by a longer or shorter period of marked depression, and in rabbit No. 39 a notable increase of weight.

INJECTION AND INGESTION OF SILICA WITH ELECTROLYTES.

Generality of the Action of the Electrolytes and the Other Colloids Upon Silica in Solution in Water.

The action of the electrolytes upon colloidal silica or the contemporaneous action of silica and the electrolytes in the animal organism deserves to be studied and understood, because it is able to account for the circumstance that silica in potable water is in some instances noxious and in others not.

It is noted that an infinitesimal quantity of carbonate of calcium coagulates a somewhat concentrate solution of silica, by a certain diastasic or enzymatic action, the disproportion between the quantity of material coagulated and the coagulant being very great. It was noted also that the coagulating action of carbonate of calcium was diminished in proportion as the concentration of the solution of silica diminished, so that the coexistence side by side of two antagonistic substances is possible, without apparent alteration and in the presence also of not the smallest quantity of the coagulant. In this case there was certainly far less diastasic action of the carbonate and the colloid perhaps against a combination with a larger quantity of the electrolyte which it could not separate. That this is true explains the fact that in most potable waters silica and carbonate of calcium are found without the least sign of alteration or separation of either substance.

Moreover, the experiments upon animals, which we will hereafter describe, agreed with our views, because they, injected with a solution of colloidal silica and at the same time with a solution of carbonate of calcium, did not present disturbances of any character no matter how long the period of the injections or the number of the injections themselves. That is to say that there is formed in the body of the animal, as *in vitro,* a collodial combination between the silica and the carbonate of calcium, sufficiently stable, so that it is eliminated in the urine or in the feces without decomposition; because it this does not occur, or this combination is broken up into its components, the separated substances have the power to act independent of each other either by absorption or by elimination. And if it is understood that the silica is a colloid, and that as such it is absorbed, and eliminated with greater difficulty than when it is combined with carbonate of calcium, there is reason to believe that the silica, introduced in this form is able to exert, sooner or later, its injurious action.

On the other hand, we are not able to say that there is not a combination of silica and carbonate of calcium which is not toxic; because as an electrolyte, acting upon a solution of coloidal silica in increasing quantity, first coagulates, then breaks up the coagulum, and then coagulates again, so it is possible that the toxicity and non-toxicity of the silica alternates with the increasing quantity of carbonate of calcium.

These considerations obtain also with the other electrolytes which may come in contact with the silica, with this difference, that each combination with a different electrolyte presents different properties. Either the combination may be noxious, as the silica in distilled water, or more or less in case it be labile and the electrolytic combination innocuous; it may be more noxious, in case it be labile and the electrolyte produce disturbances on its own account; it may be innocuous in case the combination be stable and in this case perhaps the electrolyte will not be noxious on its own account.

Besides the electrolytes, the silica may combine with either a mineral or organic colloid and then we may be able to find either an augmentation or an inhibition of the action of the silica, according to whether the new combination is more noxious than the silica alone or does not have any noxious effect. With this at the most, if the combination of the colloid silica with the other colloid is stable and if the colloid combined with it can not be substituted with an electrolyte, we will see the action of the combination remain constant in spite of the exciting or neutralizing electrolytes present. Only, by the combination of the silica with organic colloids the action may be somewhat different, because of this combination, once having penetrated the animal organism, the organic part may be oxidized and destroyed and the mineral part or the silica remain in full activity.

For this reason, the existence of natural waters, for example, with identical effects and very different composition, even completely opposite, because of the substances which accompany the silica, is a fact which should not destroy the deductions well founded and in appearance contradictory, but form a simple exception, which ought to be accurately examined and studied. And it is for this reason that we consider unjust the criticism of Gosio (2) who did not understand how silicious waters which are drunk everywhere, could be in a special condition to cause disease only in a pellagrous zone and not throughout the whole country (3). This is because in the one the silica has no obstacles to its action or does not form compositions which neutralize its action, as in the other. Wherever, with respect to the silica contained in the water, the larger centers are to be found in the same condition as the smaller and the country, not having a water which man is able to modify so easily, and which he is inclined to accept as coming from nature, with the assurance not always given, of a chemical analysis, which ordinarily is not permitted, if not a remote and uncertain provision.

An example will make our idea clearer.

There is a natural water which corrodes lead more or less actively, and which also possesses this property that less and less mineralized the more nearly it approaches distilled water, the prototype of corrosive water. And it is also demonstrated that the cause of the corrosion is the oxygen of the air, dissolved in the water so that only a trace is found. Therefore, while all waters contain oxygen, not all, but a very few, corrode lead, and among those which do not corrode there are not a few with a very slight mineralization. Thus the water of Fiuggi, which contains 5.80 gm. of fixed substance in a hectoliter, does not corrode lead at all, while the water of S. Martino of Cimino, containing 11.20 of fixed substance in a hectoliter corrodes energetically, the water of the new reservoir of Onano with 14.67 of fixed substance corrodes less energetically and the water of the old reservoir of Onano with 18.85 of fixed substance corrodes slightly. So it would seem that the conditions in which water is found to corrode lead and which have less fixed material do not have the greater power and that regarding the mineralization, is absolutely inverse. Therefore, also in this case, from the corrosion of the lead there is formed an oxyhydrate which passes into the water in solution and in colloidal suspension (4) and in it can be observed plainly the action, the quality and the quantity of the mineral substance in solution as the quality and quantity of this contributes to reinforce, to moderate or to counteract the action of the silica on the animal organism. In fact, distilled water containing 0.25% of nitrate of potassium, corrodes lead with a continuous action, but if a diastase intervene, the product of the reaction or the oxyhydrate will not pass into the water and remains coagulated in layers; but water containing nitrate of 0.5% will not corrode lead, or if it corrodes the smallest amount at first, it is arrested (5), however long the duration of the immersion.

In the face of these facts, and of others which fill the literature of colloids, it should not be thought *surprising* at most, we hope, that *most extensive regions* should be immune from pellagra, because the chemical constitution of the terrain is such as to permit electrolytes to pass into the water in such quality and quantity as to inhibit the action of the silica, just as there are very extensive regions which furnish a water which will not corrode lead.

Hence, to demand of us to state precisely "the typical composition of a pellagrogenic water" is the same as to demand precisely the typical composition of a water which corrodes lead, at which not a few Italian and foreign experimenters have not yet arrived after much study. But such an omission does not justify the denial of the facts, and does not justify the objections made to us, solely not to recognize the truth. In other words, we are able to state that *the typical pellagrogenic water is a solution of silica in distilled water, just as the typical water which corrodes lead is precisely distilled water.* Near to the two may be adapted water modified with electrolytes in different quantity, with different mixtures and in different proportions and with organic and mineral colloids; some of which act in a positive sense, others in a negative. To state precisely the figures of such a water is the same as to state precisely the number of possible combinations with the action in one sense or the other and this is not possible to do so easily or so accurately at the beginning of a research.

Meanwhile, we present, as discreet, the analysis of the water which is drunk at Onano, a city of the province of Rome, where *pellagra is definitely in the inhabited center and not in the country.*

		New reservoir	Old reservoir
Residue at 100.........	%	0.1519	0.1900
Residue at 180.........		0.1467	0.1885
Silica..............	SiO_2	0.0610	0.0520
Calcium	Ca	0.0103	0.0196
Magnesium	Mg	0.0035	0.0057
Alkali	Na	0.0049	0.0134
Chlorin	Cl	0.0089	0.0240
Sulfuric acid	So_4	0.0049	0.0155
Residue by conductibility		0.1365	0.1795

From this it will be seen that the silica in the water of the new reservoir is nearly half of the fixed substance in solution and in the water of the old reservoir is nearly one-third. The inquiry adopted has also revealed that the quantity of carbonates is very small as the quantity of the bases determined is small, one portion of which should serve to neutralize the chlorin and sulfuric acid.

The alumina was in a quantity not determinable, at least in the residue of one liter of water, which was the largest quantity which we had at our disposal.

Therefore our position is encouraging, because it will not be thought an extravagance in the case of the presence of not a few pellagrins in a center where silicious water is drunk, since it has been demonstrated experimentally that silica is the cause of the gravest disturbances, similar on the whole to those recognized in the pellagrous.

Notwithstanding, we are not able to state that the water of Onano is a true type of pellagrogenic water, because it may be possible to find active silica in water of very different composition, for the reasons explained above. Therefore, we believe that it is necessary to subject the water of pellagrogenic areas to an accurate study, an especial examination, to ascertain *what may be the special conditions which maintain the silica active in each of them.* So we have arrived at the conclusion that the most typical pellagrogenic waters ought to differ among themselves in the time in which they produce the objective symptoms of the intoxication and perhaps also in a manner to explain the intoxication itself, because certainly each combination of colloidal silica still noxious, ought to correspond in its own action.

EXPERIMENTS WITH COLLOIDAL SILICA WITH THE ADDITION OF ELECTROLYTES.

In these experiments we have used only certain electrolytes which are ordinarily found in potable water, and which are able to influence the action of the silica. We desired to extend these experiments to other elctrolytes and to combinations of electrolytes, but time was wanting and we have communicated in the following the results of the experiments in course.

Injection of Colloidal Silica and of Chlorid of Sodium 0.5% and Ordinary Alimentation.

In this series of experiments, the electrolyte was mixed with the solution of silica because it was not coagulated or heated by the chlorid of sodium.

42. Guinea pig, weight 520 grams.

On the 18th of December commenced to inject in the peritoneum on alternate days, 1 c.c. of a solution of silica and chlorid of sodium.

On the 26th of December the guinea pig aborted.

On the first of January, after a few days of an abundant *defluvium* of hair, there was noted on the back and the chest spots distinctly hairless where the underlying skin was desquamating abundantly, but the general state remained satisfactory, at least in appearance.

On the 20th of February there was manifested a notable prostration with loss of appetite and a discrete diminution in weight. This abnormal condition lasted a few days until on the 10th of March the guinea pig ate its accustomed ration and did not present further discomfort. Still the falling of the hair persisted and the number and dimensions of the hairless spots increased; on the 10th of April they embraced the two flanks and a line along the back and one encircling the chest. Moreover the belly appeared rather hairless generally, with red telangiectasic spots scattered here and there (Fig. 9).

This condition lasted till the 18th of June. The animal in this period lost appetite, became sad, the hair became hard, the skin in correspondence to the hairless zone became reddened, clear and tense. The walk was embarrassed and the hind legs dragged. The 30th of June the animal fell over and was seized with clonic-tonic convulsions and died during a convulsive attack on the morning of the first of July.

Duration of the experiment, 194 days.

Number of injections, 84.

Table of weights:

December	30,	1912,	490 grams.
January	8,	1913,	470 grams.
January	22,	1913,	420 grams.
February	26,	1913,	320 grams.
March	26,	1913,	380 grams.
April	22,	1913,	380 grams.

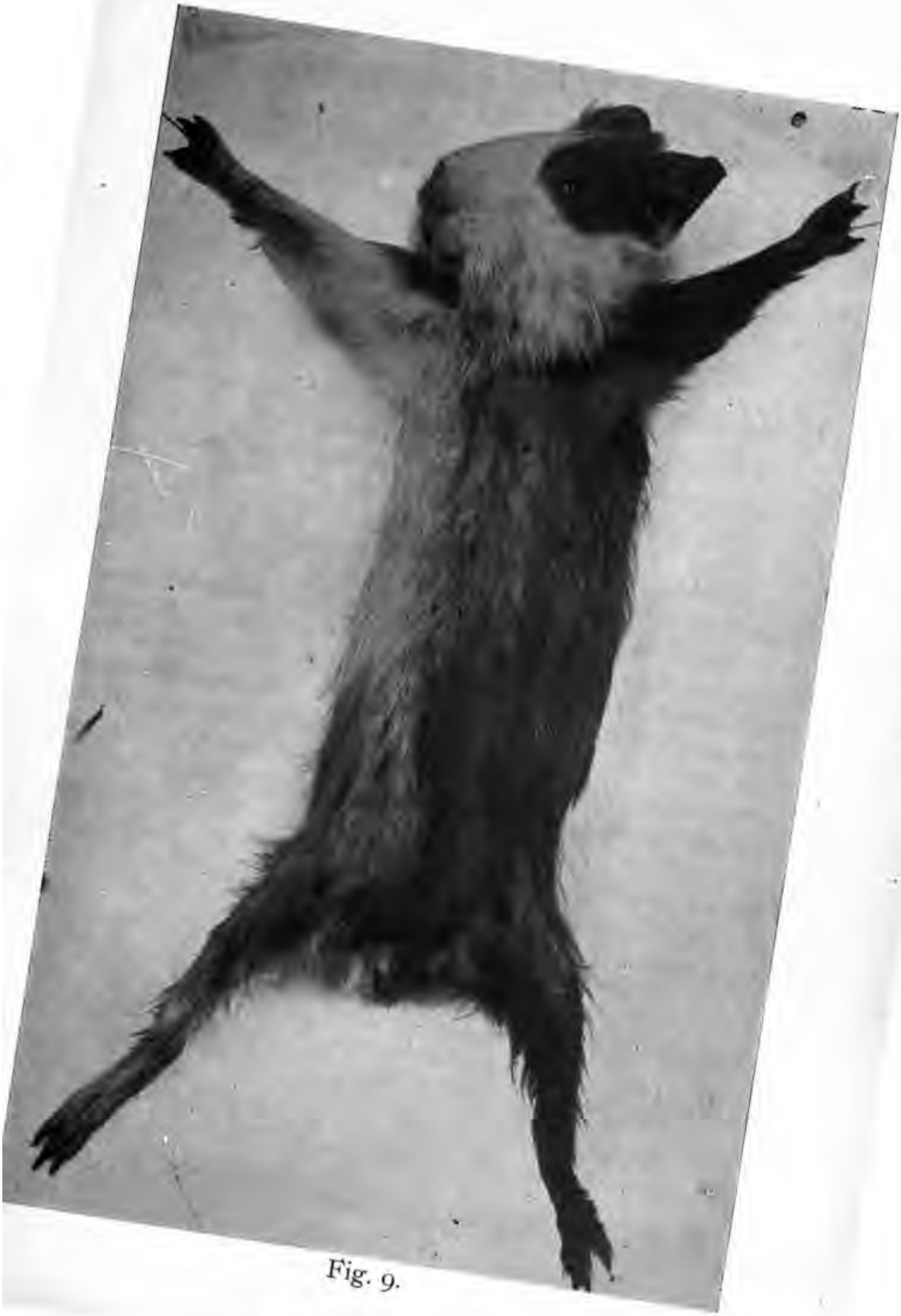


Fig. 9.

May	14, 1913,	370 grams.
June	11, 1913,	350 grams.
July	1, 1913,	260 grams.

Autopsy. (Made at once after death). One hairless spot of the size of one centimeter on the chest, two symmetrically disposed on the flanks, one linear on the back. Belly almost entirely hairless with numerous epidermic scales which were very easily detached and numerous telangiectasic spots. Internal surface of the thighs entirely hairless.

Subcutaneous connective tissue very thin; muscles dry, flaccid, opaque, stuck together.

Internal organs dry; opaque; serosa parchment like.

Heart flaccid, spleen normal; liver congested.

Kidneys somewhat congested; suprarenal capsules with hyperemia of the cortex.

Intestinal tract intensely injected, arranged like the crown of a rosary. Some zones were dilated with the walls thin, transparent, others were contracted and the walls thick. The mucosa, especially of the duodenum and the small intestine, was scattered with zones of punctiform hemorrhage.

Stomach with very weak and transparent walls which broke with the least traction. The stomach presented hemorrhagic zones of old and very recent date. They were very numerous.

Meninges injected, brain congested, soft.

Marrow of the long bones dark red.

43. Rabbit, weight 1,450 grams.

Commenced the experiment the 18th of December by injecting into the peritoneum on alternate days, 2 c.c. of a solution of silica and chlorid of sodium.

The rabbit resented the treatment at once, because he became prostrate and very thin. There was abundant defluvium of hair and by the 9th of January, after 10 injections, hairless spots of various sizes were noted disposed symmetrically on the body, especially on the flanks. The epidermis fell off in the form of shining white scales leaving to view the underlying skin smooth, whitish, thin.

There was a loss of appetite, which accompanied this state succeeded by an excessive bulimia, also the emaciation was plain to the eye.

At the same time the hairless spots increased and by the 31st of January it was evident that the posterior limbs were perfectly bare, especially on the dorsal side of the feet in the metatarsal region.

Died in the night between the 31st of January and the 1st of February.

Duration of the experiment, 44 days.

Number of injections, 20.

Table of weights:

December 30,	1912,	1,340 grams.
January 8,	1913,	1,300 grams.
January 22,	1913,	1,290 grams.
January 31,	1913,	1,000 grams.

Autopsy. Emaciation excessive. The skin, especially on the limbs, with spots and extensive hairless zone. The tissues were arid; the muscles flaccid, pale.

Scant fibrinous exudate at the place of inoculation and along the tract of the intestines which were slightly adherent to each other.

Heart flaccid. Blood contained in it, liquid, not coagulated.

Lungs normal. No pleural or pericardial liquid.

Liver slightly congested with a small nodule of coccidiosis in process of calcification. Spleen normal.

Kidneys hyperemic. Suprarenal capsules with intense hyperemia of the cortex.

Tract of the intestine intensely injected with a hemorrhagic zone in the serosa which also extended into the mucosa. Duodenum with very thin hyperemic walls with the mucosa completely covered with hemorrhagic specks.

Stomach with walls very thin, transparent, except the duodenal portion greatly thickened. Mucosa with hemorrhages of ancient and very recent date, which were from the size of the head of a pin to a hemp seed.

Meninges and cortical substance of the brain intensely hyperemic.

Marrow of the long bones brownish red.

44. Guinea pig, weight 420 grams.

On alternate days, commencing on the 7th of January, 1913, practiced injections of 1 c.c. of a solution of silica and chlorid of sodium in the peritoneal cavity.

Nothing of note during the whole period of the experiment, except a falling of hair in spots and a progressive, notable emaciation.

The animal died on the 14th of February, after the refusal of food for two days.

Duration of the experiment, 40 days.

Table of weights:

January 22, 1913, 370 grams.
February 7, 1913, 330 grams.
February 14, 1913, 230 grams.

Number of injections, 18.

Autopsy. Great emaciation; extensive hairless zone on the back, also on the sides of the body.

Tissues dry, muscles pallid, flaccid, dry.

Scant fibrinous exudate throughout the intestinal tract.

Heart, lungs, spleen normal. Blood pale, not perfectly coagulated.

Liver, kidneys and suprarenal capsules hyperemic.

Intestinal mucosa here and there congested with hemorrhagic spots.

Stomach with the walls thin, with intense hyperemia of the mucosa and a zone with punctiform hemorrhage.

Brain and meninges hyperemic.

Marrow of the long bones brownish red.

45. Rabbit, weight 1,520 grams.

Commenced the experiment on the 7th of January, 1913, by injecting in the peritoneum of the animal, on alternate days, 2 c.c. of a solution of colloidal silica and chlorid of sodium.

Almost from the beginning, that is after seven days of the experiment, there was noted a falling of the hair from spots on the back with intense epidermic desquamation. At the same time emaciation commenced and the beast became sad, indifferent, apathetic and ate very little.

At the 10th injection there was noted an incoordination of gait and the hind limbs were dragging. Complete paralysis of the hind limbs was manifest only three days before death, which occurred on the afternoon of the 5th day of February, after the animal had been for two days without urination or defecation.

Duration of the experiment, 29 days.

Number of injections, 14.

Table of weights:

January	22,	1913,	1,440 grams.
February	5,	1913,	1,470 grams.

Autopsy. (Made immediately after death). Cutaneous alterations as described above, which also have extended to the inner side of the legs.

Subcutaneous tissue thin; muscles pale, flaccid, dry.

The abdomen being opened, there was evident at once the enormous dimensions of the bladder which occupied almost the entire abdominal cavity, reaching up to the stomach and displacing all the organs. The urine contained in it amounted to 200 c.c. The rectum was also distended and full of round hard feces very dry, covered with a dense stratum of whitish mucus.

Heart full of uncoagulated blood, flaccid; the spleen was normal. The liver on the contrary was congested; the kidneys and suprarenal capsules hyperemic.

Notable hemorrhage was observed in the serosa of the intestine and of the bladder.

Intestinal mucosa as much of the duodenum as of the small intestine, the large intestine and the colon with hemorrhagic zones.

Stomach entirely empty with thin walls very transparent and with the mucosa specked with hemorrhage of ancient and recent date. Meninges injected. Cerebral surface intensely hyperemic with punctiform hemorrhage on the lower surface of the parietal lobes.

Marrow of the long bones brownish red.

46. Dog, weight 5,280 grams (female).

Commenced the experiment the 20th of December by injecting under the skin 2 c.c. of a solution of colloidal silica and chlorid of sodium.

The animal ate bread and baked dough and drank Pia or Marcia water of Rome.

Up to the 15th of January did not present anything remarkable.

On this day in making the injection we observed that the left flank presented a hairless spot of the size of about two centimes which left to view a notable epidermic desquamation.

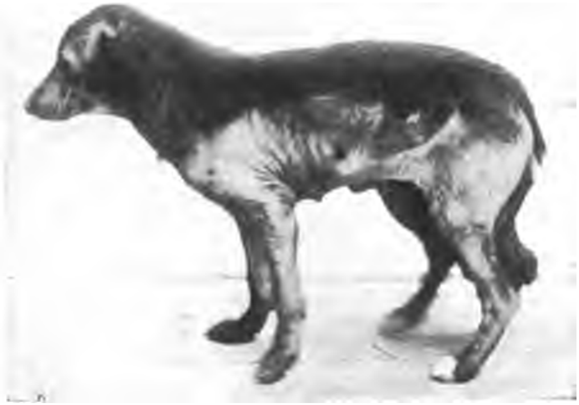


Fig. 10.

At the same time there was an abundant *defluvium* of hair. This in turn was localized in the region of the elbows (right and left) and new spots were forming on the two sides of the body.

It manifested a great thirst; at one time drank continuously for two minutes and 30 seconds; there was observed afterward a notable grade of emaciation.

The hairless spots on the belly and sides of the thorax became confluent (February 10) and these regions (Fig. 10) were almost completely bare.

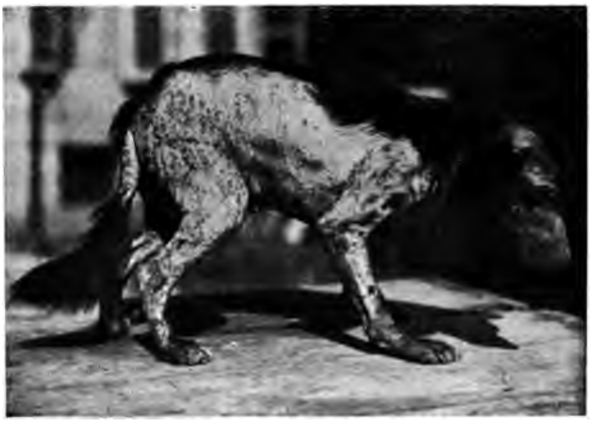


Fig. 11.

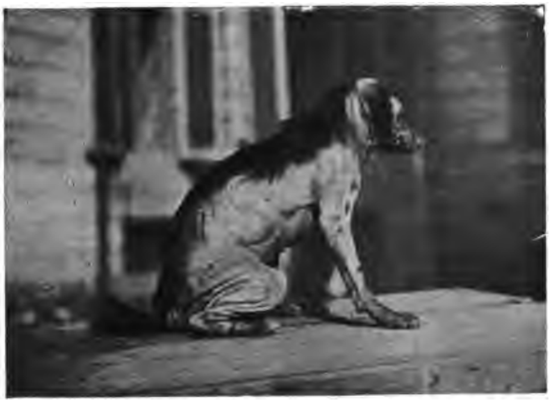
An examination of the scales, and of deep scrapings of the skin was absolutely negative with regard to parasites both animal and vegetable. This depilation was progressive and with it the emaciation and prostration increased.

The animal remained voluntarily hid from the light, scarcely responded to a call and fed very little.

A period of diarrhoea followed (February 28 to March 7) to which succeeded a period of normal feces.

The animal with *defluvium* of hair became almost completely bare (March 20) (Fig. 11) and the skin presented a marking of very minute vesicles full of serous or sero-sanguinous liquid which produced pruritus and the animal scratched often, and with the excoriation produced scabs. Where the animal could not reach to scratch, the skin peeled off in large scales. Microscopic examination of the scabs and of the epidermic scales were always negative with respect to parasites.

At the same time the skin lost its connection with the subcutaneous connective tissue (Fig. 12) and rolled up in hard wrinkles.



(Fig. 12)

On the 2nd day of April, after a day of diarrhoea, an intense fever followed (41.8 degrees), the animal is prostrate, dispnoeic.

Little by little the fever diminished, the diarrhoea ceased and the animal discretely improved. The appetite returned and with it a certain state of well being.

On the 10th of April it was noted that some fine, atrophic, dry hair was returning to the flanks, also an increase of the depilation of the back. Notwithstanding the nutriment which the animal ate, the progressive emaciation continued. It was unrecognizable, stood constantly with the head and tail down, the eyes watered and the pale lips dribbled an abundant stringy saliva.

The prostration increased to a point where the dog was no longer able to stand, it refused food and was feverish.

Reduced to a pitiable state it was killed on the 7th day of May.

Duration of the experiment, 139 days.
Number of injections, 59.
Table of weights:

January	7,	1913,	5,300 grams.
January	22,	1913,	4,950 grams.
February	20,	1913,	4,500 grams.
March	20,	1913,	3,820 grams.
April	16,	1913,	3,800 grams.
May	7,	1913,	2,950 grams.

Autopsy. Panniculus adiposus discretely preserved. Muscles pale, falccid, opaque. All of the organs pale.

Serosa dry parchment like.

Heart, lungs, liver, spleen, kidneys and suprarenal capsules somewhat pale but normal in appearance.

Intestine empty and walls flaccid, full of frothy catarrhal liquid with bloody streaks.

Intestinal mucosa intensely hyperemic with numerous hemorrhagic spots.

Stomach empty with the mucosa intensely congested, a violet red stippling of punctiform hemorrhage.

Meninges and cortical substance of the brain hyperemic. Marrow of the long bones dark red.

47. Dog, weight 4,070 grams (female).

Kept the dog under observation from the 12th of February to the 26th of March to establish the normal composition of its urine. During this period administered to the dog as food bread moistened in Pia or Marcia water of Rome.

From the 26th of March injected daily 2 c.c. of a colloidal solution of silica and chlorid of sodium.

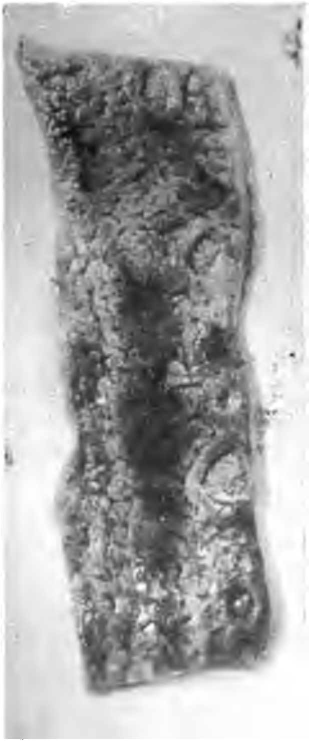
The animal, except an uniform *defluvium* of hair did not present other phenomena worthy of note, until after the middle of April, when it was noted that the paws were shedding more abundantly, leaving in view the red underlying skin, hyperemic and covered with small vesicles full of a serous liquid.

The animal, except the marked depilation of the feet did not present further disturbances until the 30th day of April.

On this day hematuria was noted. Examination of the urine established the presence of albumin, and of numerous leucocytes and erythrocytes. No renal elements.

The blood soon disappeared from the urine, but the albumin persisted and only disappeared on the 4th day of May.

Later it did not present disturbances of any kind. On the 15th of May killed the animal.



(Fig. 13)

Autopsy. (Made immediately after death). Weight, 4,320 grams.

Feet entirely hairless with the skin intensely hyperemic.

Subcutaneous tissue well preserved. Muscles normal but dry and sticky. Tissues very dry. Serosa dry; the pericardium alone contained a small quantity of liquid.

Heart, lungs normal.

Liver, spleen, kidneys and suprarenal capsules hyperemic.

Intestine intensely injected with a thick catarrhal stratum and with the mucosa in the whole tract of the duodenum and the small intestine intensely hyperemic and with large spots of punctiform hemorrhage. Peyer's Patches with the margins markedly raised as of tumefaction (fig. 13).

Stomach empty and the walls thin and the mucosa specked with hemorrhage of old date.

Meninges and cortical substance of the brain plainly hyperemic. Marrow of the long bones brownish red.

RECAPITULATION.

The injections of colloidal silica with the addition of 0.50% chlorid of sodium produced in the most of the animals of the experiment the same symptomatology as the silica alone. The slight differences were unimportant. None of the animals of the experiment died in a period as brief as the others died with injections of colloidal silica alone. Only one rabbit resisted only 29 days, the others, also the guinea pigs, which generally die in a short time, all survived 40 days and one attained 194 days.

One fact is very striking, that is the gravity of the cutaneous lesions. While with the injection or administration of silica alone, in either case, the cutaneous alterations were reduced to an abundant abnormal *defluvium* of hair, which was localized in determinate symmetrical spots, in this series the cutaneous lesions developed to a maximum truly remarkable.

It is well to look at the photograph of the dog to form a clear idea of the gravity of the lesions.

With the one exception of the greater intensity of the cutaneous manifestations, the addition of chlorid of sodium did not modify but only *retarded* the other manifestations, which were on the whole similar to those produced by the silica alone.

Nervous phenomena were not lacking. The loss of weight was constant in all the animals and in certain cases truly marked, as for example in rabbit No. 43, in 44 days it decreased from 1,450 grams to only a thousand and in dog No. 46, which in only 139 days decreased from 5,280 grams to 2,950 grams.

The anatomo-pathologic alterations were similar to those which we met when using silica alone.

Injection of a 0.9% Solution of Chlorid of Sodium Alone and Alimentation With Bran and Herbs.

48. Rabbit, weight 2,000 grams.

Commenced the experiment the 27th of January by injecting under the skin of the rabbit 2 c.c. of a physiologic solution of chlorid of sodium.

The rabbit did not resent, at least in appearance, the effect of the treatment; ate with appetite, and was sufficiently lively.

On the morning of the 28th day of February it was found prostrate, dispnoeic and died in the evening of the same day. The weight had decreased to 1,560.

Autopsy. (Made at once). Intense renal hyperemia; suprarenal capsules hyperemic and they and their cortex with a hemorrhagic zone.

Slight hyperemia throughout the meninges and the cortical substance of the brain.

Nothing further, at least in appearance, in the remaining organs, which presented an aspect perfectly normal.

Marrow of the long bones clear light red.

49. Rabbit, weight 1,700 grams.

Injected into the peritoneum of the rabbit on alternate days 2 c.c. of a physiological solution of chlorid of sodium. Commenced the injections the 27th of January, 1913.

The rabbit did not seem to resent the treatment in any way; there was noted only a slight emaciation.

Without any apparent symptoms, it died in the morning of the 17th of February, after 21 days of the experiment and after 9 injections, having a weight of 1,600 grams.

Autopsy. (Made at once after death). Intense subcutaneous hyperemia. Kidneys and suprarenal capsules congested and slight hyperemia of the meninges and of the brain.

Nothing in the other organs, which macroscopically appeared normal.

Marrow of the long bones a little more red than normal.

50. Guinea pig, weight 280 grams.

Injected under the skin, on alternate days, 1 c.c. of a physiological solution of chlorid of sodium, beginning the experiment the 27th day of January, 1913.

The guinea pig did not seem to resent the injections, which were continued until the 15th of February.

On the 16th day in the morning it was found dead in the cage after only 9 injections and 21 days of the experiment, having its weight reduced only a few grams (37 gm).

Autopsy. Intense hyperemia of the kidneys, the suprarenal capsules the meninges and the cerebral cortex.

All the other organs normal.

51. Guinea pig, weight 325 grams.

Injected on alternate days into the peritoneum 1 c.c. of a physiological solution of chlorid of sodium.

The first injection was made on the 27th day of January, 1913.

The guinea pig, without any apparent disturbance, died after 10 days of the experiment and after only four injections, without having diminished any in weight.

Autopsy. Only a slight hyperemia of the suprarenal capsules which presented a rather hemorrhagic spot in the cortex, and an apparent cerebral hyperemia. Nothing in the intestine, nothing in the stomach, nothing in the skin.

Marrow of the long bones clear light red.

RECAPITULATION.

In the experiments as above described, we see that as many animals died of injections of silica and chlorid of sodium, as animals injected with chlorid of sodium alone. Therefore it was uncertain whether the combination silica-chlorid of sodium acted as the sum of the noxious actions of the two components. The succeeding experiments cleared up this obscure point, for we note that the animals dead from silica and the chlorid of sodium have demonstrated on autopsy all of the characteristic findings of intoxication by silica alone, perhaps also a little aggravated. But the animals dead from chlorid of sodium alone, have shown only a hyperemia or congestion more or less intense of the suprarenal capsules and the kidneys, some hyperemia of the meninges and of the cerebral cortex, all the other organs such as the liver, the stomach and the intestine being apparently normal. Probably we have come upon a colloidal combination not so easily broken up and a toxic action superior to silica only in the herbivora, in which chlorid of sodium alone is toxic, and of a toxic action less in dogs, because, perhaps, more easily diffusible and eliminable by the urine and because in these animals chlorid of sodium is innocuous.

Ingestion of Gelatinous Silica, With the Addition of 0.50% Solution of Chlorid of Sodium and Alimentation With Bran and Herbs.

The gelatinous silica was administered, 5 gm. suspended in 20 c.c. of a 0.5% solution of chlorid of sodium and the solution mixed with the daily ration of bran.

52. Rabbit, weight 1,620 grams.

Commenced the experiment the 15th of January.

On the 22nd of January noted an abundant *defluvium* of hair with marked epidermic desquamation and also observed a certain emaciation. The depilation and epidermic desquamation were as great in spots as the emaciation was progressive.

On February 7th noted that there had been no defecation in 24 hours and on the 11th day, made to get out of the cage, it was evidently torpid and incoordinate in walking and paretic in the posterior limbs. The belly was distended and meteoric.

Defecation was abolished, yet the rabbit continued to eat with appetite. The hind quarters were completely paralyzed and the animal died on the night of the 21st.

Duration of the experiment, 38 days.

Table of weights:

January 22, 1913, 1,530 grams.
February 7, 1913, 1,390 grams.
February 21, 1913, 1,380 grams.

Autopsy. Numerous hairless spots on the back, on the flanks and on the inner side of the legs.

Belly enormously distended and meteoric. Subcutaneous tissues thin; muscles pallid, flaccid, dry, sticky.

Serosa dry, parchment like.

Intestinal tract and stomach with walls thin, very fragile, excessively distended, full of alimentary material or of feces and gas. Intense venous hyperemia. Gastric and intestinal mucosa markedly hyperemic.

Liver congested. Spleen normal. Kidneys hyperemic, suprarenal capsules normal.

Heart and lungs normal.

Cerebral meninges and cortical substance of the brain hyperemic.

Marrow of the long bones brownish red.

53. Guinea pig, weight 500 grams.

The experiment was commenced on the 15th of January.

On the 29th of January commenced to notice a considerable defluvium of hair, and a notable emaciation.

The guinea pig was found dead on the morning of the 5th of February after two days of loss of appetite and marked prostration.

Autopsy. Pseudo-tuberculosis of rodents.

RECAPITULATION.

Also in this series of experiments, the gelatinous silica, united with chlorid of sodium and administered by the mouth, intoxicates the animals in the same manner noted in the former series, except in the rabbit the symptoms were more grave, more interesting and more typical. Grave cutaneous manifestations were wanting, though manifested at first, they were soon followed by intestinal symptoms under the form of atonia and abolition of defecation and the nervous followed to complete paralysis of the hind quarters.

No less interesting was the antomo-pathologic finding, in which appeared the characteristic lesions, cutaneous, intestinal and nervous.

Therefore, it seems to confirm the idea expressed in the former recapitulation that the silica, united with chlorid of sodium,. acts as a combination and as such is more easily diffusible and also more toxic for the herbivora.

Ingestion of a 0.9% Solution of Chlorid of Sodium Alone and Alimentation With Bran and Herbs.

With this series of experiments, we desired, as in case of the injections, to establish the action of chlorid of sodium alone on the animals of the experiment, so to to separate the action of silica and chlorid of sodium from that of chlorid of sodium alone.

The solution of chlorid of sodium was mixed with the daily ration of bran.

54. Rabbit, weight 1,100 grams.

Commenced the experiment the 27th of January, 1913, by administering daily to the animal 25 c.c. of a 0.90% solution of chlorid of sodium.

The animal did not resent the treatment in any way; the treatment was continued until the 23rd of July, 1913, on which day it was killed without finding at autopsy any alterations of any kind, establishing instead the best state of nutrition and a notable increase of weight, 1,700 grams.

55. Guinea pig, weight 450 grams.

Commenced the experiment the 5th day of February, 1913, by administering daily to the guinea pig 25 c.c. of a 0.90% solution of chlorid of sodium.

Without presenting any disturbance, the guinea pig lived well till the 18th day of May, increasing in weight to 480 grams.

It died the 18th of May.

Autopsy. Very distinct hyperemia of the kidneys, the suprarenal capsules, the meninges and the encephalon. Nothing in the skin nor the internal organs, which were apparently normal.

56. Guinea pig, weight 350 grams.

Administered daily to the guinea pig 25 c.c. of a 0.90% solution of sodium chlorid. Commenced the experiment the 27th day of January, 1913. Without appreciable symptoms the guinea pig died the 3rd of February, having a weight of 390 grams.

Autopsy. Nothing of note except a hyperemia of the kidneys, the suprarenal capsules, the meninges and the cerebral cortex.

The other organs were normal in appearance.

Marrow of the long bones light red.

57. Rabbit, weight 1,580 grams.

Commenced the experiment May 20th by administering daily to the animal 25 c.c. of a 0.90% solution of chlorid of sodium.

The experiment was continued till the 30th of July, without the rabbit having presented any disturbance worthy of note, increasing in weight (1,635 gm.). It was killed.

Autopsy. Renal hyperemia without further macroscopic alteration of the other organs, which seemed perfectly normal with the exception of the liver which presented one little nodule of coccidiosis.

RECAPITULATION.

The administration by the mouth of a small quantity daily (gm. 0.22) of chlorid of sodium to the animals does not provoke grave disturbances.

The guinea pigs and the rabbits were both notably increased in weight, and during all of the time of the experiments, did not present the least disturbance, nor any symptoms which would lead to suspect a noxious action of the chlorid of sodium.

And the autopsy of the guinea pigs dead and the rabbits killed, except a hyperemia more or less intense of the kidneys, suprarenal capsules, meninges, and the cortical substance of the brain, has shown nothing of what we have established by administering silica with the chlorid in quantity much less and equal to 0.1 gram per day, as we have not observed any alteration of the skin, the stomach or the intestine.

We are able to state therefore that the chlorid of sodium administered by the mouth is much less noxious than administered by injection and repeat again the opinion that if combined with silica in a colloidal sense, that the combination is also more toxic than the silica alone.

Injection of Colloidal Silica With the Addition of 0.092% of Chlorid of Calcium and Alimentation With Bran and Herbs.

In this series of experiments an electrolyte was added to the solution of silica, because it does not produce a coagulation of the colloid, although in the quantity stated above.

58. Guinea pig, weight 440 grams.

Commenced the experiment the 7th of January by injecting under the skin on alternate days, 2 c.c. of a solution of colloidal silica and chlorid of calcium.

Without appreciable symptoms, except a notable emaciation and a progressive prostration, the guinea pig died the 10th of February after 16 injections.

Duration of the experiment, 34 days.

Injections No. 16.

Table of weights:

January 22,	1913,	460 grams.
February 7,	1913,	350 grams.
February 10,	1913,	280 grams.

Autopsy. Excessive emaciation, tissues of an excessive dryness and very sticky.

Heart normal, liquid blood not coagulated. Liver congested. Spleen normal. Lungs normal. Serosa dry, opaque, parchment like. Kidneys and suprarenal capsules intensely hyperemic.

Hemorrhagic spots were scattered throughout the whole intestinal tract; in the duodenum, the small intestine and the colon. They were present throughout the whole thickness of the walls, being visible in the serosa and the mucosa.

Along the intestinal tract, especially the small intestine, there were observed zones greatly distended and the walls so thin that they showed their frothy yellow liquid content.

Stomach empty with mucosa hyperemic and with hemorrhagic spots of old and recent date. The walls were so thin that they tore if touched.

Meninges and cortical substance of the brain injected.

Marrow of the long bones light red.

59. Rabbit, weight 1,310 grams.

Injected under the skin on alternate days 2 c.c. of a solution of colloidal silica and chlorid of calcium, commencing the experiment the 7th of January, 1913.

The animal emaciated rapidly, was prostrate very soon and refused food. After ten days and only six injections it died having decreased in weight to 1,150 grams. Two days before its death, while able to stand in the cage, besides feces, it passed a certain quantity of blood.

Autopsy. All the organs whitish pallid and excessively dry. Muscular masses flaccid. Serosa dry, parchment like. The extraordinary anemic state of the tissues was in contrast to the intestinal tract in which was noted a venous congestion.

Heart flaccid full of fluid blood not coagulated and of a red color. The serum obtained by centrifugation of the blood was red due to dissolved hemoglobin; in the bottom observed in equal parts blood and leucocytes which together constituted one twentieth of the amount of blood collected.

Except the state of pallor, nothing was observed in the liver, the lungs, the spleen, the kidneys nor the suprarenal capsules.

The mucosa of the intestine (duodenum and small) presented spots with punctiform hemorrhage. Intestinal contents diarrhoeic, muco sanguinous.

Stomach empty with walls normal, but with hemorrhage in the mucosa.

Meninges and cortical substance of the brain very anemic. Marrow of the long bones brownish red.

60. Rabbit, weight 1,250 grams.

Injected in the peritoneum, on alternate days, 2 c.c. of a solution of colloidal silica and chlorid of calcium, commencing the 7th of January.

After six injections, an abundant defuvium of hair commenced, which was localized in spots on the flanks, on the back, on the sides of the neck and the inner side of the legs (fig. 14). At the same time there was manifest a discrete emaciation and a notable loss of appetite which progressed until the very prostrate animal refused to eat. The state of anorrexia continued two days until the animal died the 13th day of February.

Injections No. 18.

Table of weights:

January 22, 1913, 1,170 grams.
February 7, 1913, 1,000 grams.
February 13, 1913, 920 grams.

Autopsy. Complete depilation of the inner side of the feet where the skin was intensely hyperemic. One hairless spot occupied about three centimeters on the median line of the back and others of various size covered the sides of the body, the flanks and the shoulders.

Tissues dry, muscles pale, flaccid, dry. Heart, lungs and spleen normal; blood pale, fluid, not coagulated.

Liver and kidneys congested; suprarenal capsules hyperemic. Some deposit of fibrin in the intestinal tract which was enormously distended with walls thin and transparent and of excessive fragility. In the serosa of the small intestine, the large intestine and the secum numerous hemorrhages which also appeared in the mucosa.

Stomach hyperemic, with a zone of venous congestion and some punctiform hemorrhage.

Meninges and cortical substance of the brain intensely hyperemic.

Marrow of the long bones dark red.

61 Guinea pig, weight 400 grams.

The experiment was commenced the 7th of January, 1913, by injecting into the peritoneum on alternate days 1 c.c. of a solution of silica and chlorid of calcium.

At once observed an abundant defluvium of hair from the body, especially on the abdomen and the inner side of the legs. Still the animal preserved sufficient vivacity and ate with discrete appetite, so that death came unexpectedly the 14th day of March.

Duration of the experiment, 66 days.

Injections No. 30.

Table of weights:

January	22,	1913,	370 grams.
February	7,	1913,	360 grams.
February	26,	1913,	360 grams.
March	14,	1913,	325 grams.

Autopsy. Abdomen almost completely depilated and the skin bare, even to a desquamation with thin clear lamellae, which left to view a discrete hyperemia which showed numerous telangiectasic spots. The epidermic scales were observed more abundant on the thighs and the skin which was observed below them was intensely hyperemic.

Tissues dry, muscles flaccid, pale, dry.

Serosa dry, parchment like.

Deposit of fibrin in the intestinal tract and distinct adherence the one to the other.

Heart, lungs, liver and spleen normal. Blood pale and not coagulated.

Kidneys and suprarenal capsules hyperemic.

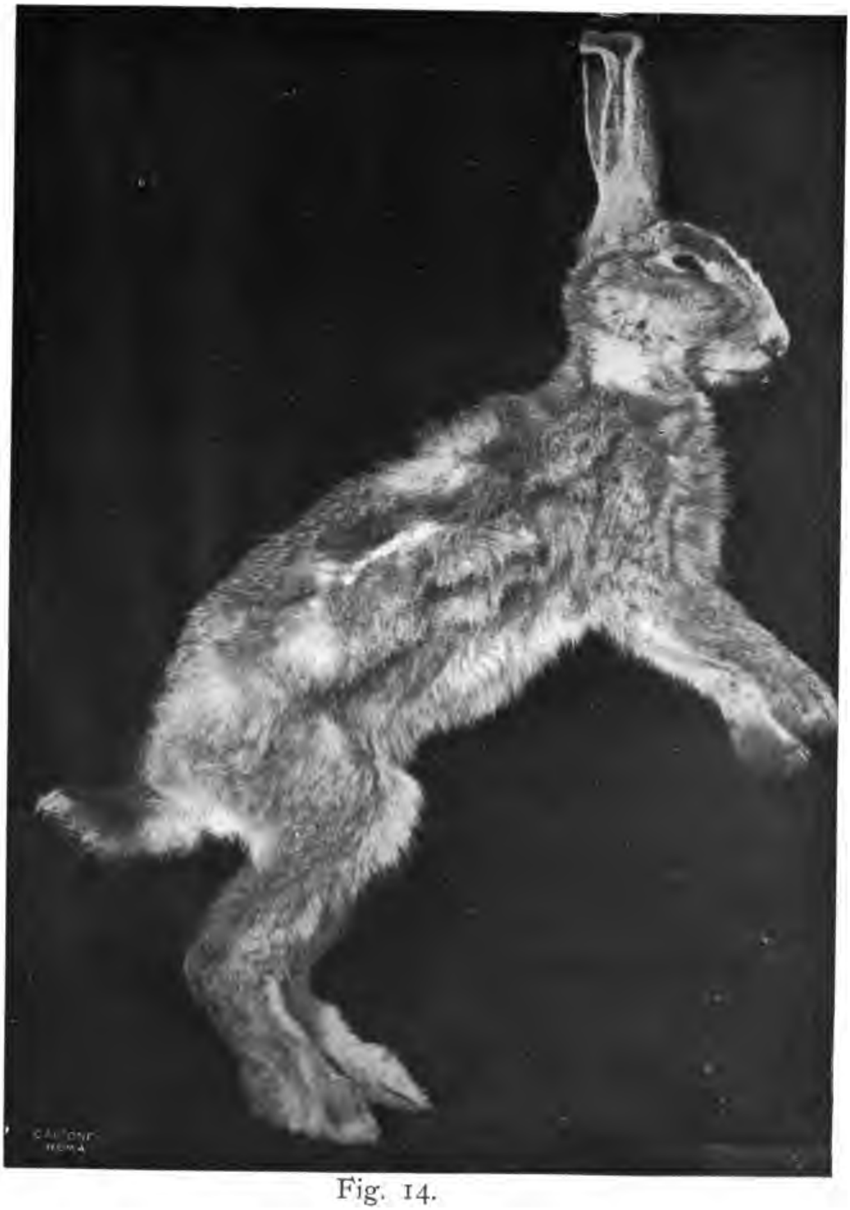


Fig. 14.

Gastric and intestinal mucosa with numerous hemorrhagic spots.

Intense hyperemia of the meninges and the cerebral cortex.

Marrow of the long bones dark red.

RECAPITULATION.

The chlorid of calcium united with colloidal silica seems to increase the noxious action, because, except rabbit No. 61, which died after a period of 66 days, the other animals died in a very short time, after having presented a notable prostration and undergone a grave depreciation, manifested after the first injections.

The necroscopic findings, while placing in evidence more or less the same alterations, with the addition of an apparent and intense anemia, demonstrate their greater gravity.

Especially grave were the alterations of the digestive system, especially in the guinea pig No. 58 and in the rabbit No. 60, in which the walls of the stomach and the intestine became so thin that they tore with the least traction.

Also in this case, we are able to repeat what we have already said about the combination silica-chlorid of sodium; that we found as before the sum of the two noxious actions or the action of one colloidal combination silica-chlorid of calcium, more fatal and quicker in its action, because it was more diffusible. It is certain that the lesions found in the animals, even in those dying quickly, were the same as those encountered in the animals intoxicated with silica alone, but more grave and more evident. This does not indicate to us that the intoxication is produced by two separate actions which certainly ought to prevail with electrolytes with their own exclusive symptomatology.

Therefore we do not hesitate to place the chlorid of calcium with the electrolytes which truly increase the action of silica.

Injection of a Solution of Colloidal Silica With the Addition of 1% of Alumina in Suspension and Alimentation With Bran and Herbs.

In this series of experiments we desired to determine the action upon the animals of a solution of silica in which we suspended a certain quantity of gelatinous alumina.

We repeat that it is not possible by the hydrolysis of silicate of alumina to obtain a colloidal solution which contains at the same time silica and alumina because the silica is antagonistic to the alumina and the presence of the one is incompatible with the presence of the other. Therefore, in potable water, which contains silica, there is not the smallest quantity of alumina in solution. But alumina is found in the muddy bottom of large or small collections of water or material, as we have stated, which renders the water turbid or opalescent.

By mixing alumina with a solution of colloidal silica we have not produced identical natural conditions, because silica, since it precipitates alumina, does not make a colloidal combination with it, although very labile, but always the combination which we have injected is a true mixture.

In every method of valuation of the effects, we have taken count of this difference.

The gelatinous alumina contained 82.60% of water.

62. Guinea pig, weight 340 grams.

Was subjected to experiment the 17th of March, 1913, by injecting on alternate days in the peritoneum 1 c.c. of a solution of silica containing alumina in suspension.

Without any apparent symptomatology, the guinea pig died on the 7th of April after 9 injections and after the duration of the experiment of 21 days, its weight having decreased to 275 grams.

Autopsy. Notable dryness of tissues.

Heart, lungs, liver, spleen normal. Suprarenal capsules somewhat hyperemic; kidneys hyperemic.

The intestinal tract distended and thin with intense hyperemia and here and there with subserous hemorrhagic spots, which were also more evident in the mucosa.

Stomach with walls so thin and transparent that they tore when only touched. In the mucosa punctiform hemorrhage was noted.

Meninges and cortical substance of the brain intensely hyperemic.

Marrow of the long bones brownish red.

63. Rabbit, weight 1,950 grams.

Commenced the experiment the 28th of February, 1913, by injecting in the peritoneum on alternate days, 2 c.c. of a solution of silica containing alumina in suspension.

After six injections and only sixteen days of experiment, the animal was found dead on the morning of the 15th of March.

Its weight had remained the same.

Autopsy. Extreme dryness of the tissues; stomach and intestinal tract much distended (fig. 15) by gas which filled it. On the surface of the stomach, the duodenum and in the jejunum, very numerous subserous hemorrhagic spots, which also extended into the mucosa.

Liver congested. Spleen normal. Kidneys and suprarenal capsules normal; bladder full.

Heart flaccid, full of liquid blood.

Lungs normal.

Meninges and cortical substance of the brain intensely hyperemic.

Marrow of the long bones dark brownish red.

64. Guinea pig, weight 550 grams.

On the 28th of February, 1913, commenced the experiment by injecting on alternate days into the peritoneal cavity, 1 c.c. of a solution of colloidal silica containing alumina in suspension.

The animal, after six injections, died on the morning of the 15th of March, having presented for a few days a marked prostration and failure of appetite, accompanied by a very discernible emaciation. Its weight on the day of death was 385 grams.

Autopsy. (Made at once after death). Subcutaneous tissue very thin; tissues excessively arid, muscles pale, flaccid, dry.

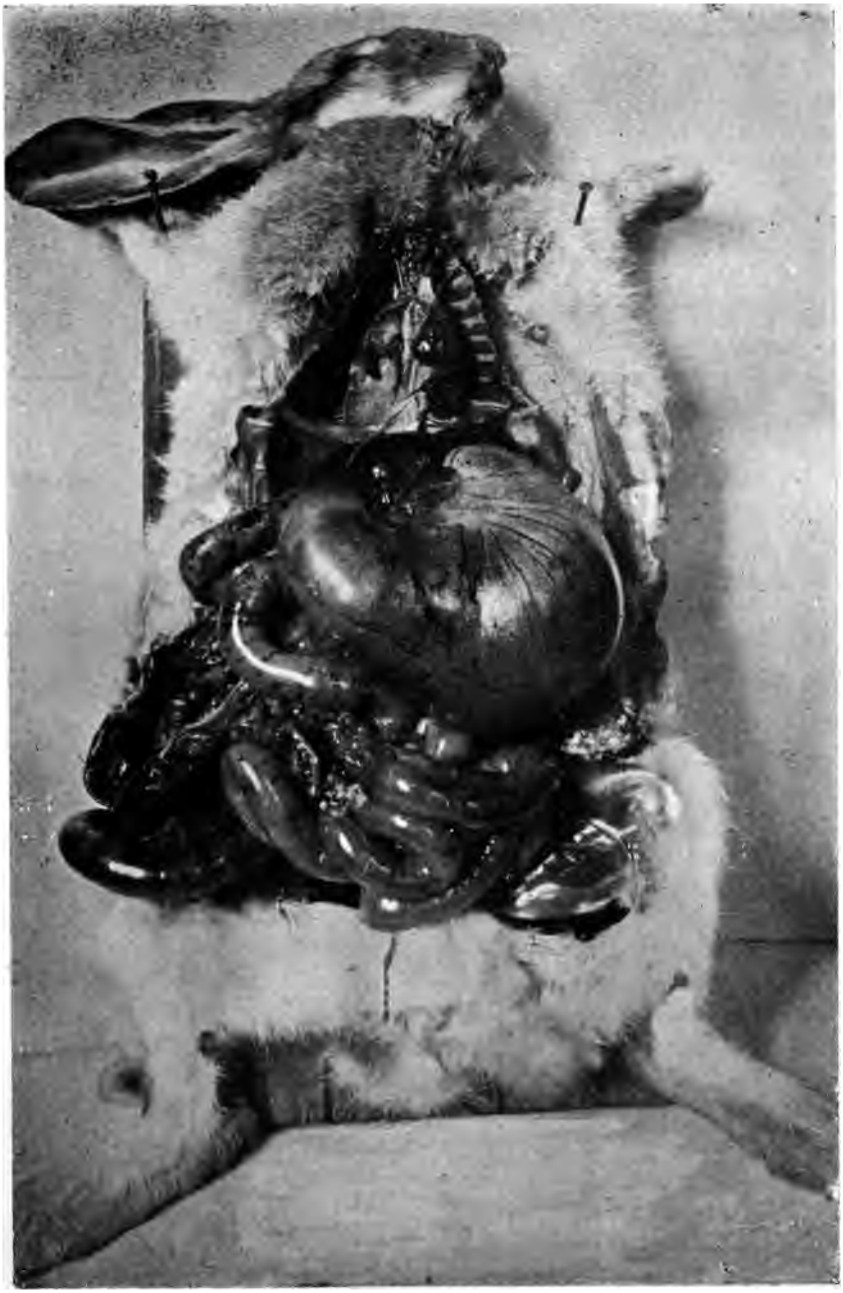


Fig. 15.

Absence of peritoneal and pericardial liquid.

Heart, lungs, liver, spleen and kidneys normal.

Suprarenal capsules with slight hyperemia of the cortex.

Intestinal tract dry, intensely injected and sticky. Mucosa intensely hyperemic with a hemorrhagic zone.

Stomach with thin walls and hyperemic mucosa and specked with hemorrhagic points.

Hyperemia of the meninges and of the cortex of the brain.

Marrow of the long bones brownish red.

65. Rabbit, weight 2,750 grams.

On the 17th of March, 1913, subjected the animal to experiment by injecting on alternate days into the peritoneum, 2 c.c. of a solution of colloidal silica containing alumina in suspension. The rabbit aborted the 4th day of April.

After the abortion remained prostrate for the day, but soon recovered; ate with appetite and became lively.

Remained in this state of well being a short time, until on the 16th of April commenced again to eat but little and to remain motionless for almost all day in a corner of the cage. At the same time it had a discrete falling of hair, which had lost its luster and softness. At the same time a considerable emaciation was noted. Taken from the cage on the 2nd of May and left free in the room, it was observed that the rabbit was no longer free in its movements. The hind quarters were rigid, extended. Ate only a few herbs, refusing the bran.

This condition grew continually worse and on the 10th day of May observed a characteristic spastic para-paretic walk with retropulsion. The spastic paresis then extended to the fore quarters, while the hair became dry, rough and the eyes blear.

The animal died in a convulsive attack, occurring at midday of the 14th of May.

Duration of the experiment, 58 days.

Injections, No. 25.

Table of weights:

March 26, 1913, 2,850 grams.

April 22, 1913, 2,320 grams.
May 2, 1913, 2,140 grams.
May 14, 1913, 1,620 grams.

Autopsy. Some hairless spots along the back. Subcutaneous tissue thin; tissues and muscles arid.

Heart flaccid, empty, with red fluid blood.

Absence of pericardial and peritoneal fluid.

Liver congested, lungs and spleen normal.

Kidneys congested, suprarenal capsules with hyperemia of the cortex.

The intestinal tract was dry, hard and full of a yellow frothy liquid which was easily visible through the thinness of the walls.

The mucosa of the duodenum and the small intestine was marked with a hemorrhagic zone.

Stomach empty with a little yellow mucus; the walls were thin and very fragile while the pyloric portion was much thickened.

The gastric mucosa was markedly congested with numerous hemorrhages of old and recent date.

The meninges and the cerebral substance very hyperemic.

Marrow of the long bones, dark red.

Ingestion of a Solution of Colloidal Silica and of Gelatinous Alumina With Ordinary Alimentation and With Bran and Herbs.

In this series of experiments it was our intention to approximate the conditions which it were truly possible to encounter in nature, that is, if silica and alumina, suspended in water, in colloidal combination or separate were able to provoke disturbances by way of the stomach.

In the bran was mixed 30 c.c. of the solution of colloidal silica and 3 gm. of gelatinous alumina.

66. Guinea pig, weight 350 grams.

The experiment was commenced the 11th of April, 1913.

During the first days nothing was noted in the animal, but on the 28th day of April it was found inert with the paunch bloated.

Remained in this condition about an hour, insensible to any stimulus. When it commenced to move it dragged its hind quarters and entirely refused food.

This abnormal condition lasted for a short time, until the guinea pig quickly changed and ate with appetite and regained its vivacious movements. This well being lasted until the 9th of June, for on the morning of the 10th found the guinea pig in grief and an extraordinary agitation; started at the least noise, tried to run away, hid under the manger and bit the iron rods of the cage. On this period of excitement followed one of depression, during which the animal shook with general tremors.

This state of hyperexcitability increased until the end and on the 30th of June, after two days of complete anorrexia, the animal died in a convulsive attack.

The experiment lasted 69 days, during which the weight of the animal decreased to 250 grams.

Autopsy. Subcutaneous tissue thin. Muscles flaccid, pale, dry and hard. Heart normal; lungs slightly congested; liver congested, spleen normal.

Kidneys distinctly hyperemic, suprarenal capsules with some punctiform hemorrhage in the cortex.

Intestines empty with walls transparent, dry, sticky; in all the mucosa of the duodenum and small intestine few spots of punctiform hemorrhage.

Stomach empty with walls extremely thin and very transparent. Mucosa with a large hemorrhagic spot in proximity to the duodenum.

Meninges and cortical substance of the brain intensely hyperemic. Marrow of the long bones dark red.

67. Rabbit, weight 1,550 grams.

Commenced the experiment the 11th day of April, 1913.

After about 20 days, noted an abundant falling of hair which was located principally on the sides of the belly and neck and along the back. On the 3rd of May there was a thermic elevation until the centigrade thermometer in the rectum registered 41.2 degrees (normal temperature 39.5).

The fever lasted a few days with a slight daily decrease until on the 8th day of May it decreased to the normal. Meanwhile the falling of hair continued and by this time observed well defined hairless spots which exposed to view the underlying skin, hyperemic, tense, clear. Marked loss of appetite.

May 12th. The animal walks incoordinate; there is a spastic paresis of all four legs which remain rigid. Incited to walk it retrocedes and falls very readily.

In the cage it stands motionless with the four feet extended and refuses food. At the same time there was an increase of the emaciation and depilation, with falling of large thin epidermic scales; they extend still further. The eyes became bleak, sunken; the skin dry, hard and the animal died on the 2nd of July, after 82 days of experiment, its weight having decreased to 1,250 grams.

Autopsy. Extreme aridity of the tissues. Muscles dry, opaque, flaccid; serosa dry, parchment like.

Heart flaccid, containing pale blood not coagulated; lungs and spleen normal; liver congested, gall cyst turgid, full; kidneys somewhat hyperemic, suprarenal capsules intensely hyperemic in the cortex.

Intestinal tract injected with a subserous hemorrhagic zone which also extended into the mucosa; walls thin, aspect moniliform.

Stomach with walls so thin that they tore with the least traction and were in contrast with the wall of the pyloric portion which attained a thickness of about one centimeter, leaving the pyloric lumen open one millimeter. In the mucosa was noted an extensive zone of punctiform hemorrhage and traces of hemorrhage of ancient date.

Meninges and cortical substance of the brain intensely hyperemic.

Marrow of the long bones dark red.

68. Monkey (*Cynocephalus papio*) young of about two years.

On the 10th day of May commenced the experiment by giving the animal to drink daily a solution of silica containing 0.7114 gm. of SiO_2 and 2.5 gm. of gelatinous alumina per liter.

Therefore there was in each liter 0.44 gm. of dry alumina (Al_2O_3), gelatinous alumina containing 82.60% of water, as already stated.

For food, gave bread, potato, herbs, some biscuit, fruit and sugar.

The monkey seemed not to resent the effect of the treatment and remained lively and well nourished. It was agile in its movements; had a good appetite and daily normal defecation.

The animal did not present any disturbance until the end of December.

From that time it commenced to become sad, and, although at first it presented all the agility and vivacity proper to such animals, it remained almost all day backed up in the most obscure corner of the cage. It moved rarely, ate with diminished appetite, and, while not apparently losing weight, was evidently suffering. The regions of the chest, the elbow, the forearm, the side of the back, commenced to present limited zones of depilation and in them the skin seemed reddened.

This condition was gradually aggravated and at the present day (first of March, 1914), the animal passes almost all of the time doubled up with the legs flexed on his belly and the head inclined between the knees. There is intense thoracic and abdominal hyperesthesia, eats listlessly and hairless spots are increased in size and number. The tail presents especially at the base of the dorsal side an extensive erythematous zone with vesicles and eruptions full of a serous liquid. The callosity was also intensely hyperemic and here and there showed small vesicles which broken in any point gave rise to a yellow scab. Whenever the skin was bare there appeared a desquamation of the epidermis in thin clear lamellae.

Injection of a Suspension of Gelatinous Alumina of 1% and Alimentation With Bran and Herbs.

69. Guinea pig, weight 420 grams.

Commenced the experiment the 17th day of March, 1913, by injecting 2 c.c. of a suspension of alumina in the peritoneum.

Nothing was observed during the life of the animal except an abundant falling of the hair. After five injections, the guinea pig died on the morning of the 29th of March, having its weight decreased in the thirteen days of the experiment to 300 grams.

Autopsy. Abdomen and inner side of the legs almost completely hairless, with the skin desquamated in thin brilliant scales.

All of the internal organs normal, except the intestine and the stomach which presented in the mucosa a somewhat hemorrhagic zone.

Meninges and cortical substance of the brain intensely hyperemic.

Marrow of the long bones dark brownish red.

70. Rabbit, weight 2,870 grams.

Subjected the animal to experiment the 17th day of March, 1913, by injecting, on alternate days in the peritoneum, 2 c.c. of a suspension of alumina.

During all the time of the experiment, which was protracted until the 11th day of June, the animal did not present any symptom other than a slight loss of appetite, which alternated with a period of normal appetite.

Only after the 22nd injection there were three days of notable prostration during which it did not pass any urine.

It recovered entirely in a short time, and in a state of apparent good health lived until the 11th of June, the day on which it died.

Duration of the experiment, 86 days.

Injections No. 37.

Table of weights:

March 26, 1913, 2,770 grams.
April 22, 1913, 2,440 grams.

May 10, 1913, 2,440 grams.
June 11, 1913, 2,270 grams.

Autopsy. (Made at once after death). Aridity of the subcutaneous tissues. Muscles pale and flaccid.

No pericardial nor peritoneal liquid.

Heart, liver, lungs and spleen normal.

Slight hyperemia of the kidneys and the suprarenal capsules.

Intestinal tract empty of food, full of a frothy greenish liquid, very hyperemic. Mucosa of the duodenum, of the small and large intestine hyperemic with a zone full of punctiform hemorrhages.

Stomach full of mucus with the walls thin and with the mucosa scattered with hemorrhagic spots.

Meninges and cortical substance of the brain slightly hyperemic.

Marrow of the long bones brownish red.

RECAPITULATION.

Gelatinous alumina, injected into the animals at the same time with silica, seems to reinforce the noxious action of the latter; because the course of the intoxication is notably abbreviated in comparison with that of the silica alone, and the toxic phenomena are much more grave.

In fact, the rabbit No. 65, in only 58 days has given a complete picture of the phenomena; from the depilation to the spastic paralysis, and at the autopsy, has presented all the alterations characteristic and noted as ascribed to the digestive system, to the meninges, to the brain and the skin. The other animals sickened and died in a very short time, showing at the autopsy the lesions notably aggravated which were recognized in the animals dead from intoxication with silica alone.

Gelatinous alumina, ingested by the guinea pigs and the rabbits at the same time with the silica, has produced the same effects as have the injections, with the only difference of the prolongation of the same effects. In the monkeys, instead, after about 11 months, disturbances commenced to be manifested, clinically identical with those observed in the other monkey which drank water with silica alone.

Gelatinous alumina alone produces by injection the same toxic picture as the silica, at least in the herbivora used in this experiment, with the difference of the alterations lacking in the liver and the atrophy of the musculature of the stomach and the intestine which were almost constant in the animals treated with silica alone and with silica and alumina. Another difference was in the great sensibility shown by the guinea pigs for alumina while the rabbits on the other hand were most sensitive to silica.

Therefore, we are able to state that *alumina concurs to aggravate the intoxication of the silica,* by adding to it its own concurrent action. But we are not able to state the same conclusions concerning the combination colloidal silica alumina, because we have not only not the proper experience, but we are not able to explain otherwise from the belief that the colloidal combination would be labile, this property being very variable in the different colloids.

Besides, we are not able to affirm that the noxious action of alumina, as revealed in the guinea pigs and the rabbits, is maintained in the higher animals, although, from what we know, we would hesitate to state the contrary. On the other hand, intoxication by silica in man will not be influenced by alumina except in turbid or opalescent water, because in ordinary limpid and potable water it is always contained in very small, and as we say, negligible quantity.

Contemporaneous Injection of a Solution of Colloidal Silica and of Carbonate of Calcium and Alimentation With Bran and Herbs.

For this experiment we have prepared a solution of carbonate of calcium by passing for a long time a current of carbonic anhydrid in a suspension in distilled water of carbonate of calcium recently precipitated and accurately weighed. The solution was quickly filtered into a flask of Jena glass, then sealed in ampules of 1 c.c.

This solution contained 0.0696 gm. of carbonate in 100 c.c. and the experiments on the animals were made by injecting in the peritoneum at the same time and separately the solution of silica and the solution of carbonate, thus avoiding the coagulation of the silica which would have happened through contact with the carbonate in the water.

71. Rabbit, weight 1,600 grams.

Commenced the experiment the 9th of January, by injecting on alternate days, 2 c.c. of a solution of colloidal silica and 1 c.c. of a solution of carbonate of calcium into the peritoneal cavity.

Thus, the animal having received daily a quantity of SiO_2, equivalent to 0.01423, and of CO_3Ca, equivalent to 0.01392 gm., survived until the 28th of April, on which day it was killed, after having received 48 injections.

During all the time of the experiment the weight of the animal remained about the same and on the day of death was 1,590 grams.

Autopsy. Except for a distinct fibrinous exudate at the point of injection, nothing of note could be observed. All of the organs normal and those of the abdomen well moistened with peritoneal liquid.

72. Guinea pig, weight 290 grams.

Commenced the experiment the 9th day of January, 1913, by injecting on alternate days on one side 1 c.c. of a solution of colloidal silica and on the other 1 c.c. of a solution of carbonate of calcium.

Without appreciable symptoms and without apparent alterations, the animal died the 17th of January after 9 days of experiment and 5 injections, its weight having decreased to 190 grams.

Autopsy. Nothing was found but a congestion of the liver. All of the other organs normal.

RECAPITULATION.

The animals subjected to experiment in this series were too few; yet sufficient to demonstrate that the carbonate of calcium, injected separately but at the same time, nullifies the noxious action of the silica in the proportion above stated. In fact, the rabbit had 48 injections without resenting the effect and without receiving any injury. At the autopsy the animal killed did not present any of the alterations of the organs produced by silica alone, except a fibrinous exudate corresponding to the point of inoculation.

The same thing cannot be said of the guinea pig, although subjected to the same injections, because it died after 9 days of experiment and we do not know whether by the action of silica and carbonate of calcium together, to which, in this case, it might have been very sensitive, or to the action of carbonate of calcium alone or to some accident.

In any case, it was notable that at the autopsy the signs of intoxication with silica were not found except a congestion of the liver, by which it is demonstrated that the carbonate of calcium entirely neutralizes the action of the silica.

For lack of time it was not possible to ascertain the exact quantity of carbonate of calcium which renders inactive a determined weight of silica and when after giving a quantity of carbonate of calcium one ought to commence to consider the silica active and toxic. This we reserve to communicate in a short time.

Injection of a Solution of Colloidal Silica and of Carbonate of Sodium.

With this series of experiments, we had in mind to demonstrate whether the action of carbonate of calcium upon silica extended to carbonate of sodium, or to the carbonates as a class.

For this, we have injected into the animals at the same time and separately by the method given above, one solution of silica containing 0.7114 gm. of SiO_2 per 100 and one of carbonate of sodium containing 0.4, 0.8, or 1.6 gm. per 100.

a. Contemporaneous Injection of Colloidal Silica and a Solution of Carbonate of Sodium 0.4%. Alimentation With Bran and Herbs.

73. Guinea pig, weight 570 grams.

Injected, on alternate days, in the peritoneal cavity 1 c.c.

of a solution of colloidal silica and 1 c.c. of a solution of carbonate of sodium, commencing the 12th of February.

During the whole period of the experiment the guinea pig did not present any appreciable disturbance. On the 4th day of March it was found dead.

Duration of the experiment, 20 days.

Number of injections, 9.

Table of weights:

February	26,	1913,	420 grams.
March	4,	1913,	410 grams.

Autopsy. No alteration of the skin; subcutaneous infiltration of serous liquid which was very abundant in the peritoneal cavity. Slight fibrinous exudate along the intestinal tract in proximity to the points of injection.

Heart normal containing fluid blood not coagulated.

Liver, spleen, kidneys normal. Suprarenal capsules enlarged with hyperemia of the cortex.

Lungs congested; abundant pleural and pericardial liquid. Intestine normal; stomach full of food not completely digested and without appreciable alterations.

Meninges, encephalon and spinal cord normal.

Marrow of the long bones red.

74. Rabbit, weight 1,860 grams.

Injected on alternate days 2 c.c. of a solution of colloidal silica and 1 c.c. of a solution of carbonate of sodium in the peritoneal cavity, commencing the experiment the 12th of February, 1913.

The rabbit did not resent the effects of the injections until two or three days before death, during which it showed loss of hair and refused food. It died on the 26th day of April.

Duration of the experiment, 75 days.

Number of injections, 32.

Table of weights:

February	26,	1913,	1,860 grams.
March	26,	1913,	1,880 grams.
April	24,	1913,	1,840 grams.

April 26, 1913, 1,810 grams.

Autopsy. Except for a very slight venous injection in the intestinal tract and abundant pleural, pericardial and peritoneal liquid, nothing was found to justify the death.

All the organs of normal aspect.

75. Guinea pig, weight 480 grams.

Commenced the experiment the 5th of March by injecting in the subcutaneous tissues on alternate days 1 c.c. of a solution of colloidal silica and 1 c.c. of a solution of carbonate of sodium.

The guinea pig, without presenting apparent disturbances of any kind, lived till the 11th day of June, 1913, on which day it died.

Duration of the experiment, 99 days.

Number of injections, 43.

Table of weights:

March 26, 1913, 480 grams.
April 22, 1913, 500 grams.
May 14, 1913, 490 grams.
June 11, 1913, 470 grams.

Autopsy. Tissues slightly infiltrated with serous liquid, which was also found in discrete quantity in the pericardium, the pleura and the peritoneum.

Slight pulmonary congestion.

Nothing appreciable in all the other organs which presented a normal aspect.

76. Rabbit, weight 1,650 grams.

Injected subcutaneously on alternate days 2 c.c. of a solution of colloidal silica and 2 c.c. of a solution of carbonate of sodium.

The first injection was made on the 5th day of March, 1913.

To the day of death (May 2) nothing happened except a loss of appetite and prostration which preceded death about ten days.

Duration of the experiment, 59 days.

Number of injections, 26.

Table of weights:

March 26, 1913, 1,700 grams.
April 22, 1913, 1,680 grams.
May 2, 1913, 1,610 grams.

Autopsy. Skin and subcutaneous normal. Slight infiltration at the point of injection.

Abundant pleural, pericardial and peritoneal liquid.

Slight pulmonary congestion, especially on the left.

Nothing appreciable in the remaining internal organs, the meninges, the encephalon, and the marrow of the bones which were normal in appearance.

b. Contemporaneous Injection of a Solution of Colloidal Silica and of an 0.8% Solution of Carbonate of Sodium. Alimentation with Bran and Herbs.

77. Guinea pig, weight 550 grams.

The guinea pig on the 12th day of February was subjected to injections in the peritoneum on alternate days of 1 c.c. of a solution of colloidal silica and of 1 c.c. of a solution of carbonate of sodium.

After four injections the guinea pig died on the 20th day of February, its weight having decreased to 450 grams.

Autopsy. (Made immediately after death). Muscles and subcutaneous tissue markedly infiltrated with serous liquid.

Slight fibrinous exudate along the intestinal tract, on the spleen and on the lower left lobe of the liver.

Very abundant sero-sanguinous liquid in the peritoneal and pericardial cavities.

Liver, lungs, spleen normal.

Heart flaccid, full of liquid blood, pale.

Kidneys hyperemic, suprarenal capsules much enlarged with some hemorrhagic points in the cortex.

Slight venous injection of the intestinal tract, the mucosa of which presented nothing abnormal.

Stomach normal and half full of food.

No hyperemia of the meninges and encephalon.

Marrow of the long bones red.

78. Rabbit, weight 1,200 grams.

Commenced the experiment the 12th day of February, 1913, by injecting on alternate days in the peritoneal cavity 2 c.c. of a solution of colloidal silica and 1 c.c. of carbonate of sodium.

The animal lived until the 26th of April without presenting any disturbance which claimed our attention.

There were made 32 injections and during the 73 days of the experiment the weight continually increased and reached 1,530 grams on the day of death.

Autopsy. Slight fibrinous exudate in correspondence to the points of injection, along the intestinal tract, and serous infiltration of the tissues.

All the other internal organs: meninges, brain, spinal cord and marrow of the bones, in appearance, perfectly normal.

c. Contemporaneous Injection of a Solution of Colloidal Silica and of a 1.6% Solution of Carbonate of Sodium. Alimentation with Bran and Herbs.

79. Guinea pig, weight 430 grams.

Subjected the animal to experiment the 12th day of February, 1913, by injecting on alternate days into the peritoneum 1 c.c. of colloidal silica and 1 c.c. of solution of carbonate of sodium.

After 16 days of experiment and after 8 injections the animal died in the afternoon of February 28, presenting a diminution of weight which on the day of death was 320 grams.

Autopsy. Subcutaneous tissue thin, infiltrated, as were the muscles, with a serous liquid.

Peritoneal liquid abundant, pericardial scarce.

Heart flaccid, full of fluid blood, not coagulated.

Lungs, especially the left, very much congested.

Liver, kidneys and suprarenal capsules congested; these with a somewhat hemorrhagic zone in the cortex.

Intestine, stomach, meninges, encephalon normal.

Marrow of the long bones red.

80. Rabbit, weight 1,920 grams.

Commenced the experiment the 12th day of February and practiced on the animal on alternate days, injections of 2 c.c. of colloidal silica and of 1 c.c. of carbonate of sodium, into the peritoneal cavity.

Except a loss of appetite and a slight prostration, occurring two or three days before death (26th of April, 1913), the animal did not present appreciable symptoms during life.

Duration of the experiment, 74 days.

Number of injections, 32.

Table of weights:

February	26,	1913,	1,905	grams.
March	26,	1913,	1,820	grams.
April	22,	1913,	1,850	grams.
April	26,	1913,	1,880	grams.

Autopsy. Distinct fibrinous exudate in correspondence to the points of injection and a serous infiltration in the subcutaneous tissues and muscles.

Nothing else of note. All the internal organs of normal appearance.

RECAPITULATION.

From this series of experiments certain facts not wanting in interest come out clear.

The guinea pigs are more sensitive than the rabbits to the action of carbonate of sodium, as we have already seen with the carbonate of calcium; since, except one which lived 99 days, the others died in a relatively shorter time, always losing weight rapidly and constantly.

The rabbits, on the other hand, lived many more days, losing in weight but a few grams, or in one case (No. 78) increasing by 300 grams.

In short, with the guinea pigs as with the rabbits, although they received a notable quantity of colloidal silica, there have been none of the external manifestations observed in the others treated with silica alone; no falling of the hair, no intestinal disturbances, no nervous alterations.

Death occurred unexpectedly, without special symptoms, or at most, preceded by a slight loss of appetite and prostration.

At autopsy we never found cutaneous alterations nor characteristic lesions of the digestive tube or the nervous system; we found only a serous exudate and infiltration never found in the preceding experiments in which dryness of the tissues and the serosa prevailed.

Therefore, we are able to state with assurance that the death of the animals did not occur because of the action of the silica, but simply because of the carbonate, which was excessive in each case. Hence the necessity of continuing this series, maintaining always constant the quantity of silica and decreasing the quantity of the carbonate below 0.4% to a non-toxic dose but which will neutralize the action of the silica, or by using other alkaline carbonates less noxious than the sodium.

INGESTION OF THE WATER OF A PELLAGROUS ZONE.

Ingestion of the Water of the Territory of Gualdo Tadino and Ordinary Alimentation and Bran and Herbs.

To complete, in the best manner possible, our experiments, and the better to meet natural conditions, we have subjected to experiment certain animals, to which we have fed the water which is drunk in a pellagrous zone of Gualdo Tadino, mixed with a certain quantity each day of the ration of bran. This water, obtained from the reservoir in the same manner which the farmers employ, was always turbid, and left standing remained opalescent.

In the bottom of the reservoir was seen a relatively abundant deposit of argillaceous material mixed with vegetable detritus.

The animals were given this water, after it had been stirred up, so as again to suspend the deposit, and thus meet the same conditions although somewhat exaggerated, as the farmers found in the region above mentioned.

Four specimens of *Macacus rhesus* were chosen, two males and two females, nearly the same age (about two years) and of the same size, and one male and one female served as controls, the other two were subjected to the experimnt. (1)

The two controls were kept together, the others in separate cages; all had the same exposure to light and air and the same food consisting of beans, bananas, biscuit, grapes, boiled potatoes and milk. The only difference consisted in the water given to drink, while the controls were given the Pia water of Rome (Aqua Marcia) the two animals under experiment were given the water of Col d'Orto, an intensely pellagrous zone of the Commune of Gualdo Tadino.

The water of this locality, which contained many of the larva of Filaridi, which it had been suspected were the cause of pellagra, was left standing for such a time that all the larva collected at the bottom. Then the upper part was removed with a siphon, insuring by repeated observation that it did not contain larva, and this was given the male to drink. From the lower portion which contained both the deposit and the nematodes, after shaking the container, the necessary quantity was taken and given to the female to drink. In such a case if it were determined that the disease was parasitic it ought to be developed only in her, the male remaining immune.

81. Monkey (*Macacus rhesus*) of about two years; male, weight 3,200 grams.

February 20, 1911, was subjected to experiment by administering daily about 300 c.c. of water of the pellagrous locality of Col d'Orto, taken from the surface from a container in repose.

Food as stated before, abundant and equal in every respect to that of other monkeys in the Zoological Gardens.

Until the end of the month of March nothing of note was observed in the animal.

April 5. Noted here and there on the body some spots partly hairless.

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1. The four monkeys, 81, 82, 83, 84 , were those which served for one of us (Alessandrini) in the preliminary experiments tending to confirm the water origin of pellagra. (See page 33

April 15. The hairless spots are more distinct along the outer side of the arms, on the neck and at the base of the ears. The skin was hard and presented a surface of epidermic desquamation.

May 6. The hairless spots were distinct and the skin, having shed the desquamation, appeared reddened. For two days the animal had a severe diarrhoea and appeared depressed. Ate with diminished appetite and sometimes refused food entirely.

May 15. The diarrhoea ceased but the prostration continued.

June 25. Noted a slight improvement; the animal is less depressed and the appetite seems to be returning.

September 1. Notwithstanding normal alimentation the animal presents a distinct decline. The lobes of the ears were transparent, very pale, the visible mucosa was also very pale. The eyes were weak, glassy. The animal sought relief from the light turned almost constantly toward the back part of the cage.

September 20. The general conditions became continually worse. The appetite diminished and the diarrhoea returned. The animal could no longer be said to be only prostrated but suffering.

September 23. There was severe diarrhoea. Food was refused completely and the monkey laid down on the bottom of the cage in the midst of the feces.

September 25. Continues in a grave state. The animal is immobile with eyes spent and grave dispnea.

September 29. The monkey was found dead in the morning.

Autopsy. Weight 1,800 grams. Cadaver much emaciated, presented sores on the callosities of the nates. Depilation in spots on the outer sides of the arms and neck. The former rounded, irregular, the latter elongate.

The visible mucosa was extraordinarily pale. The panniculus adiposus was thin and the muscles flabby and pale. Peritoneal and pericardial fat very scarce.

Peritoneal and pericardial liquid absent. The serosa appeared dry.

Heart flaccid, empty; myocardium pale, no alterations in the parietal endocardium and in the valves. Great vessels normal.

Lungs normal, trachea and bronchi normal.

Macroscopically the thyroid and thymus did not present any alterations.

Liver pale with a shining surface and the lobules slightly distinct.

Kidneys pale, soft; the limits between the two substances medullary and cortical not distinct, but the two substances of the cortex were plainly visible, the tubuli recti and the elements of the renal lobules.

Suprarenal capsules slightly hyperemic.

Spleen and pancreas normal.

Stomach dilated, pale. The walls were very thin and by their transparency exposed their contents. In the mucosa were noted here and there hemorrhagic zones more or less extensive, more numerous and larger in the great curvature.

Small intestine with walls very thin, through transparency noted its yellow contents with numerous bubbles of gas. The mucosa was congested and numerous hemorrhagic zones were noted. The large intestine and the colon presented the same alterations, but of minor grade.

The meninges were congested; the dura mater thinned, dry, congested; the pia congested; venous injection was noted in all the cerebral substance.

In the spinal cord were found: venous injection throughout the dura as in the pia meninges and in the medullary substance.

The marrow of the bones presented, in the upper and lower diaphyses, the type of the fatty marrow, the central part on the other hand was a dark brownish red color.

Entire absence of intestinal parasites.

82. Monkey (*Macacus rhesus*), female of 28 months, weighing 2,800 grams.

February 20, 1911. Commenced to administer daily about 300 c.c. of the water of the pellagrous locality of Col d'Orto. The water contained abundant larva of Filaridae and argillaceous deposits.

Food the same as in all the other tests.

The monkey at first refused to drink on account of the impurity of the water, but finally submitted to drink daily without difficulty.

No disturbance until the end of March.

March 28. Noted a violent diarrhoea of a clear yellow color and fetid odor.

April 5. The diarrhoea continues. The monkey is somewhat prostrated but continues to eat and drink as usual.

April 20. The hair falls abundantly from the whole body and is found in tufts attached to the iron bars. The diarrhoea is better.

April 28. The depilation is localized on the arms, the elbow and the cheeks from which it extends to the neck. The back of the left hand shows an abundant epidermic desquamation with an abundant falling of hair. The local lesions have produced an intense pruritus, because the monkey continually scratches the back of the hand.

May 3. Noted an epidermic desquamation also of the right hand and the skin, where scratching had removed the scales, appeared reddened.

The diarrhoea which had ceased for a time was again aggravated.

May 15. The local conditions on the backs of the hands are improved. The redness is diminished, but it was noted that the reddish-yellow scabs which held the hairs together remained. The hairless spots on the arms and neck left to view a skin tense, clear, thin. The diarrhoea persisted and a slight prostration was observed with loss of appetite.

May 25. The diarrhoea has ceased; the loss of appetite and prostration persist. The scabs have fallen from the backs of the hands and the underlying skin is colored red, tense and clear.

June 5. The monkey is somewhat emaciated; the visible musoca is pale, the lobes of the ears are pale and transparent.

June 25. The state of depression persists; the animal withdraws from the light and remains much of the time sitting down in a corner of the cage.

July 10. The diarrhoea returned, in which were noted some streaks of blood. The emaciation and depression continues.

September 23. The state of depression continues and the diarrhoea alternates with a period of normal feces. There is a state of slight progressive emaciation. The muscular masses appear flaccid, the skin wrinkled, the eyes sunken, weak. The hair has not returned to the hairless spots. The animal ate fastidiously and always remained backed up in the cage.

October 5. The death of the neighboring monkey seems to have produced a strong impression. It has not howled since the 29th. There is a violent recurrence of the diarrhoea with streaks of blood.

October 28. There is a recurrence of diarrhoea which for a few days seemed checked; there was continuous tenesmus with painful defecation. The callosities were intensely hyperemic, the tail was hairless on almost its whole length and its skin presented numerous vesicles and blisters with reddish-yellow scabs.

November 20. The diarrhoea has not yet ceased. The prostration is evident. The animal remains backed up in the most obscure corner of the cage with its head inclined between its knees. It is sparingly nourished.

December 2. For two days the monkey has not eaten at all nor moved from its position. Is dispneic. It seems that there is an involuntary emission of feces, since they are seen to dribble from the anal aperture which is much reddened.

December 3. The monkey no longer supports itself erect. It lies on its side with the hind feet paralyzed. From time to time it cries. The emission of diarrhoeic feces continues.

December 5. The monkey died during the night.

Autopsy. Weight 1,750 grams. Cadaver emaciated with extensive sores on the callosities and on all the surface of the tail; hairless spots on the back of the hands, on the arms, on the cheeks, on the neck and shoulders; skin tense, clear, shining.

Intense pallor of the skin and the visible mucosa, except the anal mucosa which was intensely congested.

Panniculus adiposus very thin; muscles flaccid, pale. Peritoneal and pericardial fat entirely wanting.

The serosa were arid and the intestinal tract and the muscles of the thorax and of the limbs were dry and opaque.

Heart empty, flaccid with the myocardium pale and the endocardium normal. No valvular lesions.

Lungs, trachea, bronchi and peribronchial glands normal.

Thyroid and thymus apparently normal.

Kidneys somewhat congested and the two substances, medullary and cortical, barely distinct. Suprarenal capsules hyperemic.

Spleen and pancreas normal.

Stomach completely empty with walls thin and flaccid and the mucosa congested and in some points with a zone of punctiform hemorrhage.

Duodenum normal; small intestine with walls very thin with a distended zone and a contracted zone and with hemorrhagic spots more or less extensive. Large intestine markedly congested with hemorrhagic spots more or less extensive throughout its whole length. The colon also was congested with a hemorrhagic zone.

The same alterations were found in the rectum and in the rectal ampulla. There was also congestion of the cerebral and spinal dura mater, and venous injections throughout the pia and the small vessels of the cerebral substance and of the medulla.

A research most accurate to find parasites of the blood, lymphatics, muscles, connective tissues and serosa, resulted completely negative.

There was found in the secum only one *Tricocephalus* and in the small intestine two *Oesophagostoma*.

83. Monkey (*Macacus rhesus*) of about two years. Male of the weight of 2,800 grams. Control.

February 20, 1911. Selected to serve as a control the average quantity and quality of food was administered; it was given to drink only the Pia water of Rome.

From the beginning of the experiment to the 15th of January, 1912, it did not present even the least disturbance.

On the 15th day of January commenced to have a diarrhoea, ate with poor appetite and showed some prostration.

On the 22nd of January the diarrhoea had become more intense, the breathing a discrete dispnea, entirely refused food and laid down on the bottom of the cage not to rise again until death during the morning of the 25th day after only ten days of apparent sickness.

Autopsy. Weight 2,300 grams. Noted on examination of the cadaver a slight emaciation and a distinct pallor of the mucosa. There was plainly evident a diffuse pleuro-pulmonary tuberculosis with numerous pleuritic adhesions on the right side. There was noted besides a most diffuse miliary tuberculosis of the liver and the peritoneum, and tubercles were also found in the thoracic walls, especially the right.

84. Monkey (*Macacus rhesus*) female of about two years, of 2,500 grams' weight. Control.

February 20, 1911. Same treatment as No. 83. The animal from the day of the commencement of the experiment remained in apparent good health until the 4th day of April of the next year, 1912.

At that time only she commenced to show prostration, refused food and passed feces rather diarrhoeic.

The prostration progressed rapidly, intense dispnea followed, nutrition ceased and after 9 days of sickness she died the 13th day of April, 1912.

Autopsy. (Two days after death). Diffuse tuberculosis of all the internal organs.

85. Guinea pig, weight 520 grams.

On the 16th of November, 1912, commenced the experiment.

The bran was mixed each day with about 60 c.c. of water brought from the division of Morano in the commune of Gualdo Tadino, one of the most pellagrous of this commune.

During all the period of the experiment, which lasted till the 3rd day of February, 1913, there was noted a progressive prostration and decline and the hair fell abundantly, leaving denuded spots of greater or less extent on the sides of the abdomen and on the limbs.

Duration of the experiment, 80 days.

Table of weights:

November	28,	1912,	460 grams.
December	11,	1912,	450 grams.
December	30,	1912,	390 grams.
January	8,	1913,	400 grams.
January	22,	1913,	390 grams.
February	3,	1913,	310 grams.

Autopsy. Subcutaneous tissues normal. Abdominal walls normal. Muscles pale, rather dry.

Heart normal, containing liquid blood, rather watery.

Lungs slightly congested; pleural liquid scant.

Peritoneum normal; peritoneal liquid very scarce.

Small intestine distended by its liquid content and by numerous bubbles of gas. Observed in the mucosa a zone intensely hyperemic and hemorrhagic.

Stomach empty with the walls thin and with the mucosa intensely reddened especially in correspondence to the greater curvature.

Liver congested; spleen normal.

Kidneys hyperemic, without distinction between the two substances; the right with a subcapsular hemorrhagic infiltration at the inferior pole.

Suprarenal capsules with small hemorrhagic points in the cortical substance.

Meninges congested; brain and spinal cord hyperemic.

Marrow of the long bones a dark brown color.

Bacteriological examination of the blood taken from the heart resulted negative.

86. Guinea pig, weight 500 grams.

Commenced the experiment the 5th day of February, 1913, administering each day to the animal, mixed with the bran, about 60 c.c. of water taken from the division of Grello in the commune of Gualdo Tadino.

The guinea pig remained well in appearance until the end of the month of February; on the first of March commenced to lose hair, especially from the back and sides of the neck.

The hair fell from spots on the sides of the abdomen and later extended (April 25) to the whole abdomen. At the same time the appetite diminished and the animal became weak and passed the day hidden behind the rabbit with which it lived in the cage.

If the guinea pig hears a sudden sound (May 5) it starts and before it returns to a normal state has a period of greater or less length of tremor of the whole body.

The emaciation grew continually worse, the loss of appetite became more marked and the animal died in the night of the 18th of May.

Duration of the experiment, 104 days.

Table of weights:

February	15,	1913,	490 grams.
March	2,	1913,	450 grams.
March	12,	1913,	450 grams.
March	25,	1913,	370 grams.
April	10,	1913,	350 grams.
April	25,	1913,	310 grams.
May	5,	1913,	310 grams.
May	16,	1913,	290 grams.
May	18,	1913,	260 grams.

Autopsy. Subcutaneous tissue normal. Muscles pale, dry, sticky.

Heart flaccid, full of fluid blood, pale; lungs normal; no pleural liquid; peritoneum normal; no peritoneal liquid.

Intestine distended with gas but not in its whole length; has a moniliform aspect, especially in the small intestine. Is intensely injected and the hyperemic mucosa shows a zone with punctiform hemorrhage.

Stomach with transparent walls, very thin; the mucosa is hyperemic with hemorrhagic spots.

Liver congested; spleen normal.

Kidneys slightly congested; suprarenal capsules with slight hyperemia of the cortex.

Spinal and cerebral meninges injected. Cerebral cortex and medulla hyperemic.

Marrow of the long bones brownish red.

87. Rabbit, weight 1,800 grams.

Commenced the experiment the 16th of November, 1912. Mixed daily in the bran about 60 c.c. of water from Morano, a pellagrous locality in the commune of Gualdo Tadino.

From the first the animal did not seem to resent the effect of the special treatment, but increased in weight until on the 7th of February it reached 2,100 grams, but, after a few days, the rabbit commenced to eat fastidiously and appeared prostrated.

On the 26th of March the weight had decreased to 2,000 and it was noted that the animal had not eaten for 24 hours, and that extensive and numerous hairless spots were distributed symmetrically on the sides of the body, and especially on the inner side of the thighs.

Later, although eating sufficiently, it appeared more prostrated and on the 3rd of April had paraylsis of the hind quarters, involuntary emission of urine and torsion of the neck to the right.

On April 5th there was paralysis of the right fore foot and on the 8th day the fore quarters were completely paralyzed.

The rabbit died in the morning of the 9th of April. The weight was 1,700 grams. Duration of the experiment, 145 days.

Autopsy. (Made immediately after death). Numerous hairless spots over the whole body, localized, especially, on the flanks, the sides of the neck, and also on the inner side of the thighs.

The skin, where the hair was wanting, was desquamated in small scales. All the tissues were dry, sticky. Extreme leanness and the panniculus adiposus very thin.

Heart empty, flaccid, with a little fluid blood, watery; lungs normal; pleura dry, sticky; peritoneum and intestinal tract dry.

Duodenum, small intestine and colon, with intense hyperemia and here and there numerous hemorrhagic zones.

Stomach almost empty. Its scant mucous content being removed noted an intense hyperemia and punctiform hemorrhagic zones. Liver slightly congested; spleen normal; kidneys of soft consistence; no plain distinction between the two substances.

Suprarenal capsules normal.

Dura meninges cerebral and spinal injected; surface of the encephalon intensely hyperemic; spinal cord injected.

Marrow of the long bones brownish red.

88. Rabbit, weight 1,700 grams.

Commenced the experiment the 11th day of April, 1913, by administering to the animal in bran about 60 c.c. each day of water brought from a pellagrous locality called Grello in the commune of Gualdo Tadino.

Nothing special, except a slight and uniform falling of hair which was found scattered in the cage, until the end of April.

On the 3rd of May commenced to note hairless spots on the sides of the abdomen and on the inner side of the thighs.

Still the animal did not present anything abnormal, ate with discrete appetite and was as lively as usual.

On the 5th of May in lifting it up felt that the ears were warmer than usual, and taking the temperature, noted a certain elevation (40.5 centigrade) that is about one degree above the normal mean. At the same time it was ascertained that it had not defecated in 24 hours. There was some prostration.

On the following day it returned to the normal; only the prostration persisted with a certain grade of progression until the day of death which occurred in the morning of July 2nd.

Duration of the experiment, 83 days.

Table of weights:

April	22,	1913,	1,750	grams.
May	3,	1913,	1,680	grams.
May	12,	1913,	1,645	grams.
May	30,	1913,	1,580	grams.
June	10,	1913,	1,570	grams.
June	25,	1913,.	1,500	grams.
July	2,	1913,	1,490	grams.

Autopsy. (Made at once after death). Numerous hairless spots on the flanks, on the back and the sides of the neck.

Panniculus adiposus very thin and the muscles pale and dry.

The heart and the pericardium normal. The blood in the left ventricle watery, red; lungs normal; pleura opaque, hard; peritoneum opaque, dry.

Intestinal tract intensely injected. Mucosa of the duodenum and of the small intestine with an extensive hyperemic zone and spots with punctiform hemorrhage.

Stomach with walls thin in their whole extent, with the exception of the pyloric portion which appeared thickened. Noted an intense hyperemic zone and punctiform hemorrhage.

Liver congested; spleen, kidneys, suprarenal capsules normal.

Cerebral and spinal meninges injected. Surfaces of the encephalon and medulla hyperemic. Marrow of the long bones brownish red.

RECAPITULATION.

The daily administration to the animals in experiment of the water which the country people drink, from two of the most pellagrous zones of the commune of Gualdo Tadino (divisions of Morano and Grello) has provoked, although in a rather long time, the same disturbances and the same anatomopathological alterations which we met with the administration of silica or the mixture silica-alumina.

We were able to observe: the cutaneous manifestations, a notable progressive prostration and decline, a sensible diminution of weight, nervous disturbances more or less grave.

At autopsy, besides the cutaneous alterations, these were recognized: the accustomed lesions characteristic of the digestive tube, of the nervous system and of the liver.

With this it is demonstrated once again, that in the water which the country people drink in pellagrous localities a substance exists which causes grave disturbances in the animal organism, which are able to become lethal whenever they continue to use the same water and do not change the tenor of life. The perfect similarity of the toxic picture of colloidal silica with the toxic picture of the water of a pellagrous zone does not seem to be a fortuitous or accidental thing, and therefore we are induced to affirm that the toxic agent also in this water is in fact the silica in solution or the silica and the silicates in suspension.

Ingestion of Water of the Territory of Guadno Tadino (a Pellagrous Zone) and Alimentation With Corn Meal and Herbs.

This series of experiments is none other than that followed in the preceding in which there was no change except in the alimentation. And in this the animals, instead of the bran of grain, were given corn meal, yet maintaining the same ration of herbs, absolutely necessary to animals with a long intestine.

The scope determined upon was the same as already expressed in other former experiments in which the animals were given silica and corn meal and herbs. Thus to demonstrate the eventual influence of corn meal upon the course of the intoxication with water from a pellagrous region.

89. Guinea pig, weight 400 grams.

On the 13th day of December commenced to administer daily to the guinea pig about 40 c.c. of the water of the division of Morano of the commune of Gualdo Tadino, mixed with corn meal.

During the whole period of the experiment the guinea pig had no manifestations worthy of note except a distinct general falling of hair.

In the morning of the 4th day of April the guinea pig was found stretched out in the cage and died after an attack of convulsions.

Duration of the experiment, 113 days.

Table of weights:

December	30,	1912,	380 grams.
January	8,	1913,	400 grams.
January	22,	1913,	420 grams.
February	7,	1913,	400 grams.
February	26,	1913,	420 grams.
March	13,	1913,	400 grams.
March	26,	1913,	395 grams.
April	4,	1913,	330 grams.

Autaopsy. (Made at once after death). Subcutaneous tissue rather scarce; abdominal walls normal, muscles very dry, opaque, pale. Heart normal, containing fluid blood; lungs normal. Absence of pleural liquid. Peritoneum normal, absence of peritoneal liquid.

The intestinal tract, somewhat hyperemic, dry, opaque, sticky. Throughout the whole length of the duodenum and the small intestine noted a zone much dilated with walls very thin, exposing to view the frothy yellow intestinal contents, alternate with a zone restricted or contracted, in a guise to give to the whole tract of the intestine so formed a moniliform aspect.

In the mucosa noted here and there zones intensely hyperemic with small hyperemic spots, localized especially in the dilated parts.

Stomach empty with walls rather thin and intense and extensive hyperemia of the mucosa.

Liver congested, spleen normal.

Kidneys normal; suprarenal capsules slightly hyperemic.

Cerebral and spinal dura mater injected; encephalon and medulla hyperemic.

Marrow of the long bones intensely brown.

90. Rabbit, weight 2,300 grams.

The experiment was commenced the 13th day of December, 1912. The animal was given daily in corn meal about 60 c.c. of water of the division of Morano of the commune of Gualdo Tadino.

The rabbit did not present any apparent disturbance during the whole period of the experiment; only towards the last days of life it showed prostration, ate but little and passed urine involuntarily.

Died the 4th day of May.

Duration of the experiment, 143 days.

Table of weights:

December	30,	1912,	2,480 grams.
January	8,	1913,	2,450 grams.
January	22,	1913,	2,590 grams.
February	7,	1913,	2,560 grams.
February	26,	1913,	2,530 grams.
March	13,	1913,	2,500 grams.
March	26,	1913,	2,450 grams.
April	4,	1913,	2,330 grams.
April	22,	1913,	2,450 grams.
May	4,	1913,	2,700 grams.

Autopsy. Advanced pregnancy, which explains the great increase in weight during the last month of life, notwithstanding the condition of prostration and the refusal of food. Subcutaneous tissues thin, muscles dry, sticky, pale; heart normal; lungs normal; peritoneum and pleura rather dry.

Intestinal tract hyperemic but extremely dry and sticky;

in the mucosa of the duodenum, the small intestine and the colon, extensive zones with punctiform hemorrhage.

Stomach full, with walls very thin, transparent, which were in contrast with the pyloric portion which was much thickened. In the mucosa was noted an intense hyperemia and here and there a zone with hemorrhage of ancient and recent date.

Liver congested; the spleen normal.

Kidneys and suprarenal capsules normal.

Cerebral and spinal dura mater somewhat injected; encephalon and medulla hyperemic.

Marrow of the long bones brown.

91. Guinea pig, weight 380 grams.

Commenced the experiment on the 5th day of February, 1913, by administering daily in meal of maize about 60 c.c. of water from the division of Grello (commune of Gualdo Tadino).

No fact worthy of note until the 15th of April, when there was noted hairless spots on the flanks and the sides of the neck with desquamation of the surface of the skin in flakes more or less extensive. At the same time it was observed that the animal had lost some of its vivacity and much of its appetite. It remained in the most retired corner of the cage, under the manger, coiled up with the hair erect. The appetite continued to diminish to a point where the food was found almost intact each day, although it was renewed daily.

In the morning of the 15th of May it was found dead.

Duration of the experiment, 100 days.

Table of weights:

February	26,	1913,	380 grams.
March	·13,	1913,	330 grams.
March	26,	1913,	340 grams.
April	4,	1913,	300 grams.
April	22,	1913,	270 grams.
May	4,	1913,	250 grams.
May	15,	1913,	220 grams.

Autopsy. Skin of the back, flanks and inner sides of the legs with hairless spots and numerous and extensive epidermic scales.

Chest and abdomen almost completely hairless with the skin covered with small shining white epidermic scales.

Subcutaneous tissues very thin, abdominal walls normal, muscles pale, flaccid; liver congested.

Heart, lungs and spleen normal; kidneys and suprarenal capsules hyperemic.

Intestinal tract distended with walls very thin, which exposed to view on the inside a frothy yellow liquid.

Mucosa hyperemic and here and there a zone with punctiform hemorrhage.

Stomach empty with walls normal; mucosa congested.

Meninges intensely injected, encephalon and medulla very hyperemic. Marrow of the long bones brownish red.

92. Rabbit, weight 1,880 grams.

The experiment was commenced on the 5th day of February by administering each day, mixed with corn meal, 60 c.c. of water from the division of Grello of the commune of Gualdo Tadino.

The rabbit did not seem to resent the effect of the special treatment to which it was subjected until the first of May. Then it commenced to be weakened and ate less. While it consumed all the herbs given to it during the day, it refused the corn meal. This state of lack of appetite alternated with a period of normal appetite. On the 10th day of May noted that the walk was incoordinate. On the 14th of May, taken from the cage, it was further recognized that there existed a conspicuous spastic-paretic gait and the animal in a state of repose supported itself on four feet in spastic tension. The hair was opaque, rough and the eyes weak. The animal, which had refused food for two days, died on the morning of the 28th of May during a convulsive attack.

Duration of the experiment, 113 days.

Table of weights:

February 26, 1913, 1,880 grams.
March 13, 1913, 1,920 grams.
March 26, 1913, 1,920 grams.
April 4, 1913, 1,850 grams.
April 22, 1913, 1,790 grams.
May 4, 1913, 1,750 grams.
May 15, 1913, 1,670 grams.
May 28, 1913, 1,520 grams.

Autopsy. (Made at once after death). Extensive depilation on the inner side of the fore and hind limbs.

Subcutaneous tissues very thin; muscles flaccid, pale, dry.

Heart empty, flaccid, with a little fluid blood. Liver congested.

Lungs and spleen normal; kidneys and suprarenal capsules hyperemic.

Duodenum and small intestine and colon with intense venous hyperemia and hemorrhagic spots in the mucosa.

Stomach completely empty of food, with a large quantity of yellowish-white mucus. The mucosa of the stomach was intensely congested, with spots of punctiform hemorrhage; the walls were rather thin, especially at the great curvature.

Cerebral and spinal meninges intensely hyperemic. Medulla somewhat hyperemic and the brain very hyperemic, especially in the frontal lobes.

Marrow of the long bones dark brown.

93. Guinea pig, weight 410 grams.

To this guinea pig, which was chosen to serve as a control, administered each day in the morning corn meal and in the afternoon leaves of cabbage and lettuce, having first moistened the corn meal with about 60 c.c. of the potable water of Rome (Acqua Marcia).

The experiment was commenced the 13th day of December, 1912.

Without having presented any apparent disturbances the animal died in the afternoon of February 5, 1913.

Table of weights:

December 30, 1912, 400 grams.
January 8, 1913, 360 grams.
January 22, 1913, 400 grams.
February 5, 1913, 390 grams.

Autopsy. (Made immediately after death). Subcutaneous tissues well conserved; abdominal walls normal, muscles normal.

Lungs with intense congestion more marked on the right than on the left.

Peritoneum normal.

Intestinal tract normal; nothing found in the mucosa.

Stomach full of alimentary material not completely digested with walls normal and musoca normal.

Liver, spleen, kidneys and suprarenal capsules normal.

Cerebral and spinal meninges normal.

Encephalon and meninges normal.

Marrow of the long bones cherry red.

94. Rabbit, weight 1,880 grams.

To the rabbit, besides the common herbs (cabbage and lettuce) administered in the afternoon, gave on each day corn meal with the addition of about 60 c.c. of the Marcia water of Rome.

The experiment was commenced on the 13th day of December, 1912, and the animal was kept under observation until the 28th day of May, 1913, when it was killed to make a comparison with another rabbit dead on the same day but subjected to experiment about two months later (No. 92).

There was nothing remarkable present during the five months and a half of observation. The appetite remained constant and no disturbance was noted.

Table of weights:

December 30, 1912, 2,070 grams.
January 8, 1913, 2,030 grams.
January 22, 1913, 2,000 grams.
February 7, 1913, 1,900 grams.
February 26, 1913, 1,900 grams.

March 13, 1913, 1,920 grams.
March 26, 1913, 1,970 grams.
April 4, 1913, 1,970 grams.
April 22, 1913, 1,970 grams.
May 4, 1913, 1,970 grams.
May 28, 1913, 1,950 grams.

Autopsy. (Made immediately after killing). Subcutaneous tissues well conserved, abdominal walls normal, muscles normal.

Heart, lungs, liver, spleen, kidneys and suprarenal capsules normal.

Nothing was observed in the stomach, which was full of food not yet digested, and nothing in the intestine.

The meninges, the encephalon and the spinal cord were normal.

Marrow of the long bones cherry red.

RECAPITULATION.

The substitution of corn meal for bran in the alimentation of our experimental animals has not produced any notable modification.

As in the preceding experiments, there were the same disturbances and the same anatomo-pathologic alterations. The experiments only lasted a little longer and in one case there was a slight increase in weight.

The animals, on the contrary, to which were given only corn meal moistened with Marcia water of Rome and the usual ration of herbs, did not present any sign of intoxication and did not have any disturbance. The guinea pig alone of the two animals in the experiment, died after 52 days, perhaps because of the same intolerance already noted of carbonate of calcium contained in a discrete quantity in the Marcia water, and to alkaline substances in general, unlike the rabbits.

III.

REVIEW AND GENERAL CONSIDERATIONS.

Having finished the exposition of our experiments on the animals and described the syndrome and the anatomo-pathologic alterations encountered in them, the spontaneous question arises:

Whether the syndrome and the anatomo-pathologic alterations are similar to those found in the pellagrous;

Whether the symptomatology and the alterations produced in the animals with the injections or the ingestion of silica in its different states and with the ingestion of water of a pellagrous zone are parallel to the symptomatology and the alterations which are recognized in the pellagrous.

To give an answer to these questions, it is necessary to review the clinical and the anatomo-pathologic picture of human pellagra and make a comparison with the clinical and anatomo-pathologic picture of intoxication with silica.

Symptomatology. All the authorities, ancient and modern, recognize the difficulty to reduce the symptoms of pellagra to a distinct and precise picture and also recognize the difficulty to make a positive diagnosis of this disease because the manifestations are very diverse and often contradictory.

In some cases in fact, certain symptoms prevail which in other cases are entirely wanting and it is not rare to observe the course of the disease, without any characteristic symptomatology. And in such a case, a diagnosis can only be made by *exclusion,* since the various disturbances of the patient cannot be ascribed to any other morbid picture, and by *induction* only because the sufferer resides in a zone where the disease is endemic or because the others of his family, ascending, descending or collateral have paid their tribute to pellagra.

However the uncertainty is not able to confound pellagra with other diseases, especially when we take into account the case history, the onset, for the most part mild and progressive and what the symptomatology presents in the *classical triad ascribed to the skin and to the digestive and nervous systems.*

In this manner we will summarize the principal symptoms ascertained in human pellagra; those also which have more of the others rather special and characteristic:

In the greatest number of cases, the disease has a slow and progressive course; yet cases are not wanting in which, for example, those described by Box and Mott (6) the course is extraordinarily rapid. Moreover it is noted:

A sense of weakness even after the least effort; extreme weakness of the lower limbs; walk uncertain, slow, in short steps with the knees bent and the feet somewhat turned out.

The skin, which usually has a sub-icteric tint, on the exposed parts (dorsum of the hands and feet, forearm, neck, face and anterior median part of the chest) is tense, clear, reddened. The redness is accompanied by an intense itching, which becomes aggravated and forms vesicles and these break and set free an exudate; the vesicles, moreover are able to become confluent and form scabs of greater or less extent; they are able to form pustules or true ulcers. In such a case, the acute period is terminated by the formation of a scab, which falling, gives place to a new ulcer; otherwise, if the lesion is limited to erythema only, at the end of the irritative phase, the hair falls after a certain period, giving place to an exfoliation of the stratum corneum. At the termination of the exfoliation, the skin appears sometimes hypertrophic, more frequently atrophic, clear, of a brownish red with whitish winding cicatricial streaks and specked with telangiectasic spots. It loses completely its rapport with the subcutaneous tissues, becomes inelastic and rolls up in hard wrinkles.

The lips are white as if burned with an acid, almost always cracked at the corners and ulcerated. The tongue is red with numerous deep irregular fissures, which divide it into knolls and give it a muriform appearance, sometimes covered by a thick coating, sometimes completely void of epithelium. The eyes are tense, clear, with a weak expression; frequently the pupils are unequal.

The sufferers have a salty salivation, which often runs down abundantly from the corners of the mouth; suffer frequently from insatiable thirst, loss of appetite, repugnance to food or immoderate hunger. There is a sensation of tension, fullness and weight of the stomach accompanied by burning and eructations. There is severe and frequent pain in the abdomen and diarrhoea, which in grave cases, may become profuse and incontrollable. Vague sensations of heat, formication, numbness of the hands, legs and trunk; buzzing in the ears; pruritis of the body, the hands and the feet; headache, darting pains along the neck and spine; tremors of the limbs, especially the upper, and of the head.

The superficial reflexes are either normal or exaggerated; the knee reflexes are exaggerated. Frequently there is hyperesthesia; they cry out if only touched, worse on the abdomen or chest; they start at the least sound. There is an increase of the moral impressionability and of the psychic excitability; loss of memory, weakness of mind, frequent mutism, sadness, sense of terror, insomina, religious scruples and a tendency to suicide. The patient often sits doubled up with the chest on the abdomen, the knees against the pelvis and the head inclined.

In grave cases the step is tottering, frequently becoming a spastic paresis or even a true paralysis of the lower limbs.

To these symptoms may be added hyperthermia, sometimes albuminuria, and not rarely the ocular lesions, especially blepharitis, keratitis, kerato-iritis, choroiditis and retinitis.

Pathological anatomy. A very great diversity of findings exists, which very frequently are in clear contradiction of each other.

And it is easy to explain these contradictory findings, knowing that the pellagrins, frequently in a more or less advanced state of their malady, die from intercurrent disease capable of determining diverse alterations or of masking the specific.

We regard it as superfluous to linger upon contradictory data of no great importance and will confine our attention to those which are found rather constant and which are characteristic of pellagra.

The cadaver is generally emaciated with a thin panniculus adiposus, with musculature for the most part flaccid, atrophic, rarely normal. The heart is almost always small, flaccid, easily torn, with yellow or brownish-yellow pigmentation. Sometimes it is of greater volume than usual and this is due, as Lombroso well states, more to the weakening of the degenerate walls than to hypertrophy. Hence in the heart the atrophic findings predominate.

The liver is ordinarily congested, sometimes simply hyperemic, and rarely of normal appearance. On microscopic examination all the alterations of a chronic parenchymatous or an interstitial hepatitis are found. The gall cyst in most cases is found full and turgid. The kidneys, besides being generally altered, do not present anything specific; yet sometimes they show atrophy, granulation, or increase of volume with the cortical substance thickened, pale, soft, easily crushed, sometimes they show fatty degeneration, a true cloudy swelling, or such lesions as are recorded in Bright's disease.

Microscopical examination reveals rather constantly either a glomerulitis or alterations such as are considered parenchymatous or interstitial nephritis acute and chronic.

Nothing special is found in the spleen and pancreas. The alterations of the digestive tract are more constant. Generally both the stomach and intestine are very much distended by the gas inclosed or by a frothy greenish-yellow liquid.

The gastric mucosa is specked with small hemorrhages and sometimes presents hyperemia or intense venous congestion.

The walls of the stomach are almost always thin because of the atrophy of the muscular coat, which, however, in the pyloric portion is often found hypertrophic and produces, as noted by Strambio, a strong contraction of the pyloric orifice.

The gastric walls themselves are thin and at such points may be very easily torn and give place to perforation as has been observed by Carswell.

The walls of the intestine are also very thin and in the small intestine thin and distended zones are observed alternating with contracted zones, as if tied by a string, in a guise as to give the intestinal tract a moniliform appearance.

The serosa sometimes presents hyperemia with venous arborizations, which can be easily seen through the pale intestinal wall. The mucosa of the duodenum and the small intestine is almost always hyperemic with hemorrhagic zones; while the large intestine presents ulcerated zones.

Peyer's patches are edematous or tumefied.

Microscopical examination of a hemorrhagic zone generally shows extravasated blood of rather normal appearance without any surrounding reaction. In other cases necrosis is found and the intestinal villi are bare of epithelium with stroma without structure and made up of amorphous material with some disseminated nuclei.

In the nervous system, examined macroscopically, there are but few alterations; hyperemia or congestion predominates as much of the meninges as of the cortical substance of the encephalon; there is frequently noted a thickening and opacity of the membrane, with or without adherence to the cranial vault and not rarely the cerebral substance is soft, easily crushed, as well as edematous. Microscopic examination discloses diffuse congestive conditions and especially degenerative conditions more or less grave.

Having thus set out in brief the symptomatological picture of human pellagra and stated the more important anatomo-pathologic alterations, we will see what symptomatology and what necroscopic alterations are presented by the animals subjected to the action of silica in its various states, and to water brought from a certain locality the worst invaded by pellagra in the territory of Gualdo Tadino.

The animals, with the exception of a few cases in which the course of the disease assumed an acute attack, died after a rather long period of time and the picture of the disease was a slow progressive course and we may say rather chronic in those animals which had the smaller dose of silica and especially in those to which it was administered by the mouth.

The principal symptoms which were recognized in life were those characteristic of the skin, of the digestive tube and of the nervous system. The animals, more or less, all presented a notable prostration and a progressive decline. All, excepting the cases of very rapid course, showed cutaneous alterations either under the form of a simple *defluvium* of hair which was more marked in the guinea pigs, or under the form of a falling of hair from symmetrical spots, localized principally on the sides of the body, on the back, the neck and the inner sides of the thighs. The hairless skin appeared reddened with an abundant scaling of epithelium corneum in the form of shining white lamellae. Under this was observed the smooth skin white or red, atrophic.

Others instead, which were observed especially on the callosities of the monkeys, had a true erythematous dermatitis. In them the small vesicles full of liquid, running together, give place to the formation of scabs, which become in time an extensive ulcerated zone. The thick scab formed later, falls off and leaves to view a thin, clear, atrophic skin of red character. In the dogs the atrophy of the skin was noted very easily because in them (fig. 12) more than in the rabbits, it lost its elasticity and rolled up in hard folds. Telengiectasic spots were also noted (fig. 9). The mucosa always appeared pale and thin; the eyes tense and clear.

In the dogs there was generally manifested throughout the sickness an insatiable thirst and one of them (No. 46) was seen to drink continuously for two minutes and 30 seconds. There was a constant loss of appetite, especially toward the end of life, but cases were not wanting of normal appetite and of true bulimia. Frequently, in the dogs and the monkeys especially, we noted a diarrhoea which in some cases was bloody (No. 82, 11).

There was appreciable cutaneous pruritis, especially in the dogs and monkeys; a pruritis which it was not possible to attribute to animal parasites, none of which were found notwithstanding the most diligent search. Tremors, especially of the fore limbs and the head, were also constant and fibrillar tremors were very frequent especially of the muscles of the face. The cutaneous reflexes were much exaggerated; it was sufficient to touch the skin on any part of the body to observe a shaking of the whole or to see a contraction of the fore or hind limbs. There was a notable hyperesthesia; if the animals were touched on the abdomen or the chest, especially in the advanced stages of the intoxication, they reacted strongly and the monkeys and dogs emitted the most acute cries of pain. Almost all (the rabbits in minor degree) started at the least noise.

In grave cases of long duration, the normal position of the animals was much modified. The monkeys, the dogs and the guinea pigs coiled up, holding the limbs near together, and the spine curved and the first holding the head low or resting between the knees (Fig. 2). The gait, in chronic cases, is uncertain, slow, and the animal scrutinizes the ground before moving. Later it becomes a spastic paresis, with a preference for the posterior limbs (spastic paraparesis) and, in some cases, also the fore limbs and finally paralysis. This was observed especially in the rabbits in which also paralysis of the sphincters and detrusors was recognized.

In some cases, but not frequently, we recognized hyperthermia (No. 46 and 67); in one case albuminuria (No. 47); in others indicanuria (see Pathogenesis), and in another bilateral kerato-iritis (No. 10). Diminution of weight was constant and if in any case it was increased it was an apparent fact that it was not due to accretion.

The anatomo-pathologic findings were almost always constant.

Generally the bodies were very thin, almost emaciated; the panniculus adiposus was thin; the musculature pale, flaccid, atrophic, without clearness, dry, sticky.

The skin, observed under the microscope, with low magnification, appeared denuded of hair and in intense desquamation of the epidermal strata from extended ridges of the stratum corneum.

With a greater magnification it was distinctly noted that in not a few points it was barely possible to distinguish the two strata, lucidum and mucosum, because of the great thinning to which they had been subjected. Notable alterations were observed in the character of the elements which constitute the corpus mucosum of Malpighi.

For the most part, the limits of the single cell were not distinct, here and there the nuclei were scarcely colored and rounded vacuoles were often found in the corpus mucosum, due probably to the necrosis of the elements which compose it. The protoplasm of the cellular elements seemed to be in a state of regression which was from a simple cloudy swelling to necrosis, and the normal rapport of position of the elements was not preserved.

Besides in the interior of the hair follicles the normal structure was not recognized; there was observed instead the residue of the elements which compose them, forming balls of a double refracting substance slightly yellow in reflection. Inside the blood vessels which were almost always turgid to repletion with blood there was observed a more or less intense small celled infiltration with eosinophile cells. (Plate I, Fig. 2; Plate II, Fig. 1 and 2.)

The heart was almost always flaccid, with the myocardium pale; the blood contained in it for the most part very fluid.

The liver, in the greater number of cases, congested, frequently hyperemic, almost never normal.

Sometimes the kidneys did not present in appearance any alterations, again they were found soft and pale, mostly hyperemic. In some cases on microscopic examination there was noted a true glomerular and tubular nephritis, with necrosis of the epithelium of the tubules and the glomerular tract, with intraglomerular and interstitial hemorrhages, especially numerous between the tubuli recti in the medullary substance. (Plate XIII.)

Sometimes the stomach was found empty; more frequently distended by gas or by a greenish-yellow frothy liquid. Its walls, in general, were found so thin as to become perfectly transparent (Fig. 7) and ruptured with the least traction. This could not be attributed to an antemortem or post-mortem alteration, because the autopsies were generally made at once after death, and because, in the very numerous control observations, made upon other rabbits, dead in the laboratory from other causes, this was never recognized.

With the thinness of the walls was frequently contrasted, especially in the rabbits, the extraordinary thickness of the pyloric portion, which, in certain cases, attained about 8 millimeters. Also this fact was never observed in the controls, nor in numerous autopsies made on other rabbits. The serosa was generally only hyperemic, sometimes it presented vast hemorrhagic zones (Fig. 15). The mucosa was frequently intensely congested, very frequently hyperemic and almost always with hemorrhagic zones more or less extensive, some of very recent date, some also of ancient date.

Microscopic examination of portions of the stomach disclosed intense venous hyperemia, since all the veins were overfull. The glandular epithelium frequently presented alterations and in some cases was in a state of advanced cloudy swelling and in such a zone disappearance of nuclei was observed. Sometimes the mucosa presented simply a hemorrhagic infiltration, sometimes a zone with extensive hemorrhage which occupied the whole thickness of the mucosa and sometimes also invaded the muscular.

Indeed the greater and more evident alterations are characteristic of the muscular apparatus of the stomach, as characteristic of the *muscularis mucosae* as of the muscular coat, which is notably reduced in thickness. There was noted an atrophy or rather an advanced necrosis with extensive vacuolization of the muscular fibers and frequently it was not possible to recognize the normal structure of the muscular elements. (Plate V, Fig. 1.)

Without doubt, such alterations were, in some cases, much more grave than those which were found in the mucosa and in the glandular elements, which sometimes were so altered as to be said to be destroyed; since in some points only the fragments of the epithelium were noted surrounded by an abundant small cell infiltration.

The intestine was sometimes found empty and distended by gas or by a greenish-yellow frothy liquid; sometimes it was found full especially the secum and rectum, of feces and hard balls, dry, covered by a dense stratum of whitish mucus (especially in the rabbits).

The intestinal walls, in the greater number of the chronic cases, were found thinned and not uniformly, but usually a distended tract was followed by a restricted tract so as to give to the whole intestine a characteristic moniliform appearance (Fig. 8). The serosa was almost always hyperemic, especially in the duodenum and the small intestine and usually presented a hemorrhagic zone more or less extensive (Fig. 15).

The mucosa itself was sometimes only hyperemic, frequently congested, very frequently hemorrhagic. The hemorrhage was sometimes punctiform, sometimes a zone more or less extensive; in such a case it assumed such an entity as to make the whole tract of the duodenum and small intestine appear marbled.

Hyperemia and hemorrhage were often found in the secum and large intestine; only once was there found a true ulceration. Peyer's patches presented especially in the dogs, edema and tumefaction (Fig. 13).

Microscopical examinations of the intestine also showed characteristic alterations, especially of the mucosa and musculature. The musculature in fact presented a notable atrophy with cloudy degeneration, more or less marked, according to the points examined; the mucosa presented either a simple hyperemia or a distinct shedding of epithelium, or also a true hemorrhagic zone and a zone of necrosis with intercellular hemorrhagic infiltration. In these places the structure of the intestine was no longer recognized; the villi were transformed into accumulations of altered epithelium. The hemorrhage was so grave as to produce complete separation of the mucosa from the muscular coat and sometimes to invade also the whole thickness of the intestinal walls. (Plate III, IV, V; Fig. 2, VI and VII).

Everywhere there was a scarcity of white elements; this was opportune to demonstrate that the inflammatory reaction was slight.

Macroscopically there was found in the nervous system, hyperemia of the meninges which sometimes also presented congestion, or opacity. The cerebral substance was almost always found hyperemic, more or less intensely, and sometimes easily crushed and edematous.

The microscopic alterations of the nervous system have been described in the following by a competent person to whom we have intrusted abundant material for study; therefore, we are able to say at this time that in our animals, as has been observed in human pellagra, the congestive and degenerative factors predominate. In fact in the cerebral cortex, the meninges were hyperemic; the vessels full of red corpuscles, with thin walls without perivascular lymphocytic infiltration.

The nervous cells presented generally the type of chronic degeneration (Nissl); nucleus highly colored, following the contour of the cell; body of the cell elongated, nucleolus intensely colored, corpuscles of Nissl partly preserved or reduced to granules. Other cells, less numerous, presented the type of acute degeneration with the cell body swollen, vacuolized, eccentric nucleus slightly colored and the corpuscle of Nissl disappeared or reduced to very fine granules.

In the pons the vessels had thick walls, were full of blood and polynuclear leucocytes; there was notable lymphocytic infiltration, and granules of pigment and residue of destroyed blood around the vessel.

In the spinal cord the vessels presented thick walls; were full of red corpuscles and masses of fibrin, and there was sometimes slight, sometimes abundant, perivascular lymphocytic infiltration.

The cells of the anterior and posterior horns did not present grave alterations. The processes were long, thin and much ramified, the corpuscle of Nissl preserved, the nucleus central, slightly colored with the nucleolus intensely colored. In the sections prepared with the method of Bielchowsky, the neurofibrils appeared reduced to fine granules, the nucleus was central and clear, the nucleolus not colored, nothing noticeable in the fibrillar network endo—or pericellular.

In the following table we have thought it useful to collate all the more important symptoms attributable to human pellagra and to compare them, one by one, with those obtained with intoxication with silica, in order that every one may be able with facility to recognize the great similarity between the two intoxications. It is true that the symptomatologic picture of intoxication with silica, just as tabulated, is not present entirely in an animal, but it is also true that the same picture is not present entirely in the human pellagrin. Hence, the difficulty of the diagnosis of pellagra in life and the uncertainty in the assignment of the anatomo-pathologic alterations, which we have noted in the beginning of this chapter.

SYMPTOMATOLOGY OF

Human Pellagra.	Intoxication With Silica.
Attack of the disease slow and progressive, only rarely has a rapid course.	Attack of the disease slow and progressive, only rarely has a rapid course.
Walk uncertain, slow.	Walk torpid.
Presence of symmetrical crythema with frequent formation of ulcers and sores.	Depilation symmetrical, erythema with frequent formation of ulcers and sores.
Epidermic desquamation in large scales.	Epidermic desquamation in scales more or less large, thin, clear.
Desquamated skin, thin, clear, brownish red, for the most part atrophic.	Desquamated skin, thin, clear, reddened, for the most part atrophic.
Presence of telangiectasic spots.	Presence of telangiectastic spots.
Tongue in ridges bare of epithelium.	....
Eyes tense, clear, weak.	Eyes tense, clear, weak.
Thirst insatiable.	Thirst sometimes insatiable.
Loss of appetite or immoderate hunger.	Loss of appetite or hunger.
Diarrhoea.	Diarrhoea, sometimes bloody.
Pruritis.	Pruritis.

Tremors of the upper limbs and the head.	Tremors of the fore limbs and the head.
Fibrillar contracture.	Fibrillar contracture.
Reflexes exaggerated.	Reflexes exaggerated.
Hyperesthesia, overexcitation.	Hyperesthesia, overexcitation.
Depression.	Depression.
Squatting position with flexion of the thighs on the chest and the head inclined.	Squatting position with flexion of the thighs on the chest and the head inclined.
Spastic paresis in the prevalence of spastic paraparesis.	Spastic paresis in the prevalence of spastic paraparesis.
Paralysis of the lower limbs.	Paralysis of the hind limbs.
Hyperthermia.	Hyperthermia.
Oliguria.	Oliguria.
Albuminuria and indicanuria.	Albuminuria and indicanuria.
Concomitant ocular affections.	Concomitant ocular affections.

PATHOLOGICAL ANATOMY OF

Human Pellagra.	**Intoxication With Silica.**
Predominance of muscular atrophy, of points of congestion and of hyperemia.	Predominance of muscular atrophy, of points of congestion and of hyperemia.
Cadaver emaciated.	Cadaver emaciated.
Thin panniculus adiposus.	Thin panniculus adiposus.
Musculature flaccid, atrophic.	Musculature flaccid, atrophic.
Heart flaccid, easily torn, pigmented.	Heart flaccid.
Liver for the most part congested.	Liver for the most part congested.
Renal hyperemia and cloudy swelling.	Renal hyperemia and cloudy swelling.
Stomach and intestine with serosa hyperemic with venous arborization.	Stomach and intestine with serosa hyperemic with venous arborization.
Thinness of the gastric walls through atrophy of the muscular coats.	Thinness of the gastric walls through atrophy of the muscular coats.
Thickening of the pyloric region.	Thickening of the pyloric region.
Stomach and intestinal tract distended, full of gas or of a frothy greenish-yellow liquid.	Stomach and intestinal tract distended, full of gas or of a frothy greenish-yellow liquid.
Gastric mucosa hyperemic, congested, marked with hemorrhage.	Gastric mucosa hyperemic, congested, marked with hemorrhage.
Intestinal walls thin.	Intestinal walls thin.
Intestine of moniliform appearance.	Intestine of monoliform appearance.
Mucosa of the duodenum and of the small intestine covered with mucus, with hyperemic and hemorrhagic zones.	Mucosa of the duodenum and of the small intestine covered with mucus, with hyperemic and hemorrhagic zones.
Large intestine with ulcerated mucosa.	Large intestine sometimes with ulcerated mucosa.
Peyer's patches edematous, tumefied.	Peyer's patches sometimes edematous, tumefied.
Hyperemia of the meninges and of the cortical substance of the brain.	Hyperemia of the meninges and of the cortical substance of the brain.
Opacity of the membranes.	Opacity of the membranes.
Cerebral substance easily ruptured, edematous.	Cerebral substance easily ruptured, edematous.
....	Marrow of the long bones brownish red.

IV.

PATHOGENESIS.

The conclusion which results from the experiments set out and discussed is, without doubt, that silica has a noxious action on the animal organism, in whatever way and in whatever state it is introduced. Also the results of this noxious action are not due to the silica alone as a material, but rather to the state which it assumes in the water, either as a true solution or as a colloidal suspension. For this reason, desiring to inquire into the pathogenesis of this new intoxication, it is not less possible to take into account the state of the intoxicating material, as it is not possible not to take into account for examination certain facts which are presented in the various groups of experiments.

To penetrate the process by which silica intoxicates the animal organism and produces the alterations not few nor trivial which we have described, it is necessary to know the changes which eventually are able to take place in the elimination of mineral substances in the urine. Since colloidal silica as we have already seen, by combining, with greater or less affinity, with many mineral salts, has the power, as we have said, to cause them to accumulate and to alter their reaction in consequence.

Therefore, we have subjected to experiment a dog of medium size, kept in a cage adapted to collecting the urine; into it we injected daily under the skin 3 c.c. of a 0.7114% solution of colloidal silica and gave it only bread to eat and Marcia water to drink, one of the best potable waters of Rome.

For analysis, we have thought it proper to collect the urine of 48 hours and not of 24, because quite frequently in this space of time a dog in captivity abstains from urinating; this it is not able to do for the following 24 hours. Thus we have always been able to collect the urine in a sufficient quantity, and even more, for the determinations which we had proposed to make. These are: specific gravity at 15°, fixed substance, ash, chlorin, sulfates, phosfates, alkalies calculated as sodium ions.

The specific gravity was determined with a Westphal balance; the fixed substance was determined by weighing the residue of the evaporation of 20 c.c. of the urine in a platinum crucible and after drying in the oven at 100° for two hours; the ash was determined by burning the residue and heating the capsule to almost a beginning red until all the carbon disappears or until the ash appears a flaky white, avoiding fusion. The chlorin was determined directly in the urine, following the volumetric method of Volhard and the sulfates by weight, precipitated in the form of sulfate of barium. The phosfates were determined by the volumetric method, with a standard solution of nitrate of uranium, and following all the indications set out in the treatise of Neubauer and Huppert (7). The alkalies were determined in the ash of the urine by treating it with concentrate sulfuric acid and heating cautiously in the direct flame until the appearance of white fumes, at which time all the bases contained in the ash have been transformed into sulfates. Then it was totally dissolved in water and the solution treated with carbonate of barium in excess. A current of carbonic anhydrid was passed through the mixture for a long time to transform the bases liberated from the sulfuric acid, into bicarbonates; then it was thoroughly dried on a water bath in a porcelain crucible and in the oven at 120°.

The dry substance was extracted again with a mixture of equal parts of 96% alcohol and distilled water and the alcoholic liquid filtered and caught without loss in a weighed platinum crucible. This, after acidification with hydrochloric acid, was evaporated on the water bath to dryness and the residue cautiously heated to fusion. The crucible, after cooling in the desiccator, was weighed again and the difference in weight determined the quantity of alkaline chlorids, which, by an easy calculation, were transformed into sodium ions and referred to one liter of urine.

The results are arranged in the following table, separated into four periods. 1. Normal composition of the urine in captivity. 2. Composition of the urine under the action of injections of colloidal silica. 3. Composition of the urine after the suspension of injections of silica. 4. Composition of the urine under the action of renewed injections of silica.

TABLE Ia.

In One Liter of Urine.

FIRST PERIOD.

Date 1913.		Vol. of Urine c. c.	Sp. gr.	Fixed Substance gm.	Ash. gm.	Cl. gm.	SO_4. gm.	PO_4. gm.	Alkalies Na. gm.
Jan.	1.	190	1.0218	44.85	10.60	3.76	1.488	3.553	3.015
	3.	180	1.0237	41.40	10.48	4.63	1.375	3.052	3.862
	5.	140	1.0230	32.74	11.87	6.00	1.266	3.341	4.105
Mean.		170	1.0228	49.66	10.98	4.79	1.376	3.315	3.660
				SECOND PERIOD.					
Jan.	10.	124	1.0355	96.98	7.950	1.348	1.843	3.056	2.739
	12.	98	1.0476	141.73	7.450	0.900	1.427	4.915	2.140
	14.	80	1.0500	144.90	4.420	0.638	2.498	3.965	1.038
	16.	104	1.0520	150.00	6.600	1.418	6.248	5.782	3.224
	18.	40	1.0490	134.96	2.140	0.752	5.988	1.652	0.408
Mean.		89	1.0468	133.71	5.712	1.011	3.600	3.874	1.909
				THIRD PERIOD.					
Jan.	20.	53	......	50.52	5.680	2.021	2.532	6.773	1.243
	22.	33	......	135.68	11.080	4.254	7.196	10.325	2.198
	24.	75	1.0320	53.10	13.340	8.176	3.022	4.873	4.824
	26.	110	1.0306	50.93	14.830	14.442	3.351	3.799	5.294
	28.	86	1.0340	66.25	17.250	7.018	3.462	2.478	3.116
	30.	140	1.0443	53.18	4.510	3.190	4.930	3.717	1.760
Mean.		83	1.0332	68.27	11.115	6.516	4.082	5.327	3.072
				FOURTH PERIOD.					
Feb.	12.	40	1.0550	125.25	17.300	1.560	6.875	13.919	6.197
	17.	80	1.0542	122.30	25.500	7.304	3.054	13.628	4.336
Mean.		60	1.0546	123.77	21.400	4.432	5.964	13.773	5.266

In the urine of the 2nd, 3rd and 4th periods indican was always found in greater or less quantity, except on the first days of the second period.

A comparison between the figures, setting forth the mean composition of the urine in captivity and the mean composition of the urine voided by the animal during the period of injections, places in evidence first of all, a diminution of the volume of urine which decreased from 170 c.c. to 89 c.c. and an increase of specific gravity which from 1.0228 arose to 1.0468. This seems to demonstrate that under the action of the silica the organism feels less need of water and therefore voids less and more concentrate urine. Therefore, if count is taken of the fixed substance contained in the volume of urine of 48 hours, it will be seen that this has increased from 6.852 to 11.700; that is to say that the increase of specific gravity was not exclusively due to the concentration of the urine, but to an actual increase of the substance in solution. On the contrary, the mineral substance of the 48 hours was diminished by more than half, having decreased from 1.853 to 0.568, and the salts retained or less eliminated; the chlorin decreased from 0.798 to 0.096; the phosforic residue from 0.565 to 0.329; the alka-

In the Total Volume of Urine.

Fixed substance gm.	Ash gm.	Cl. gm.	SO_4 gm.	PO_4. gm.	Alkalies Na.	Sum of ions total vol.	Dif. in ash and ions.
			FIRST PERIOD.				
8.521	2.014	0.714	0.283	0.678	0.573	2.248	—0.234
7.452	1.886	.833	.248	.549	.695	2.325	—0.439
4.583	1.661	.847	.177	.468	.575	2.067	—0.406
6.852	1.853	0.798	0.236	0.565	0.614	2.213	—0.359
			SECOND PERIOD				
12.025	0.986	0.167	0.229	0.379	0.339	1.385	—0.128
13.889	.730	.088	.140	.282	.209	1.263	+0.011
11.592	.354	.051	.199	.317	.083	.877	—0.306
15.600	.686	.147	.650	.601	.335	1.164	—1.047
5.398	.085	.030	.240	.066	.016	.399	—0.267
11.700	0.568	0.096	0.291	0.329	0.196	1.017	—0.347
			THIRD PERIOD.				
2.678	0.301	0.107	0.134	0.358	0.066	0.976	—0.675
4.477	.365	.140	.237	.341	.073	1.035	—0.670
3.982	1.001	.613	.227	.365	.362	1.829	—0.828
5.602	1.631	1.588	.368	.418	.582	3.256	—1.625
5.697	1.483	.603	.298	.213	.268	1.535	—0.052
7.445	.631	.447	.690	.520	.246	2.276	—1.645
4.980	0.902	0.583	0.325	0.369	0.266	1.818	—0.917
			FOURTH PERIOD.				
*5.010	0.692	0.062	0.275	0.557	0.025	1.318	—0.626
**9.780	2.040	.584	.404	1.090	.346	3.206	—1.166
7.395	1.366	0.323	0.339	0.823	0.185	2.262	—0.896

*After 5 injections.
**After 10 injections.

lies from 0.614 to 0.196. The sulfuric residue, on the contrary, was augmented, since from 0.236 it increased to 0.291; so that the salts alike retained in great quantity are the chlorid of sodium which the alkaline phosfates closely follow.

This by the mean: but if with the figure representing the day of the experiment as abscissa and the composition of the urine of each separate day of the experiment as an ordinate, we trace a system of coordinate rectangles or a curve, we still see that the sulfuric residue (Fig. 16) although it was not passed in equal measure with the chlorids (Fig. 17), and with the phosforic residue (Fig. 16) follows the same oscillations as they, with one emission more elevated than the corresponding chlorin and phosforic residue, and which notably influenced the mean. It is also important that the phosforic residue is eliminated in the same manner as the chlorin, differing from

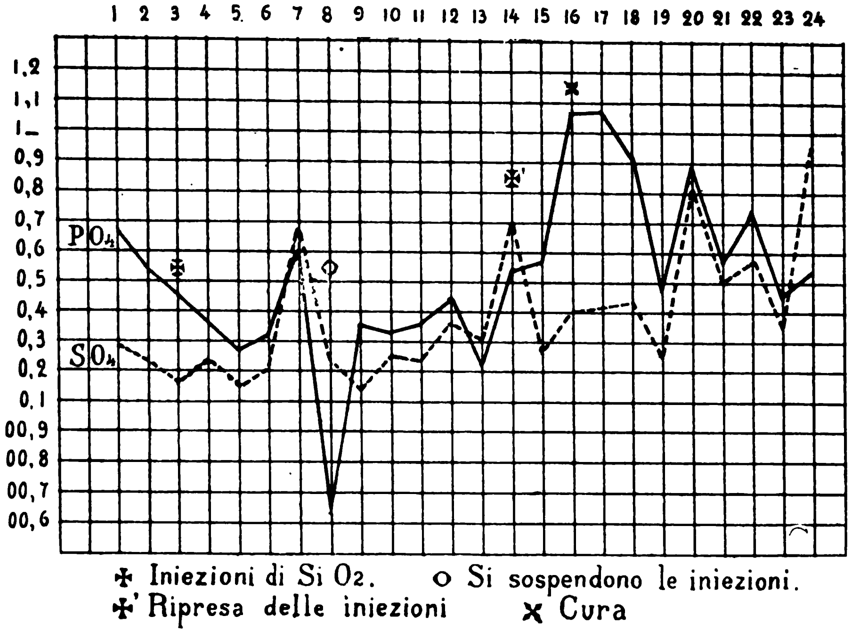


Fig. 16.

what occurs in anemia, cancerous cachexia, chronic nephritis, etc., in which for an increase of the chlorin there is a diminution of the phosforic residue, and agreeing with what occurs in

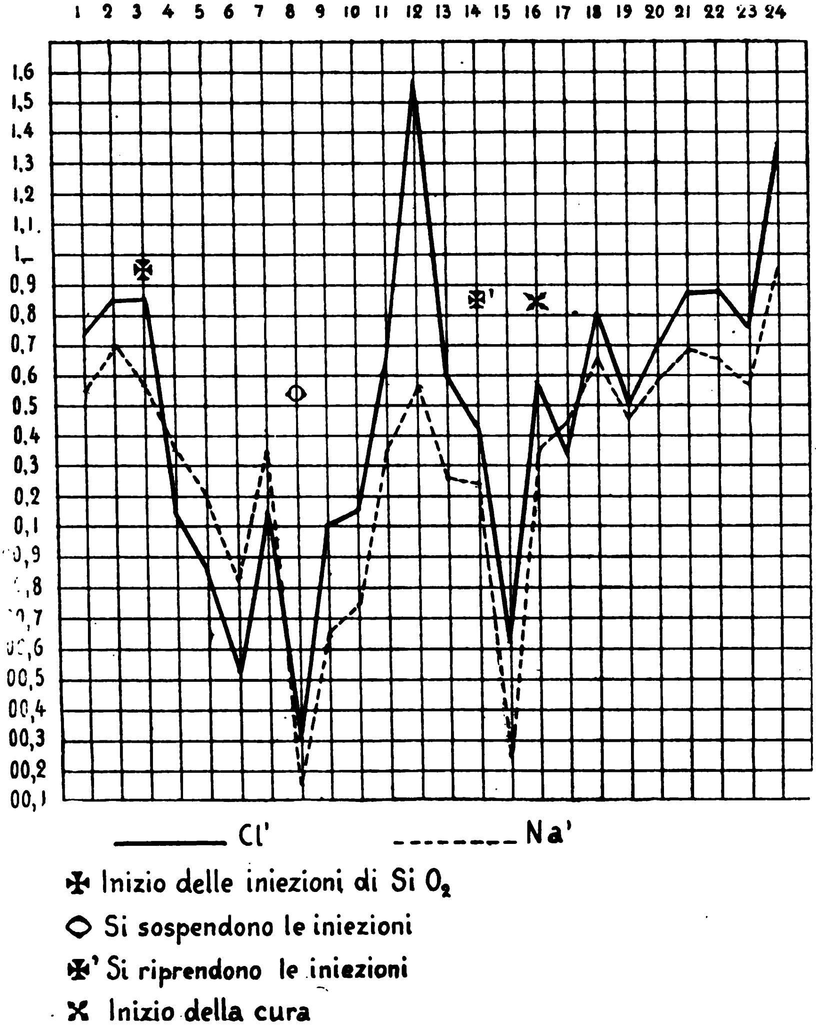
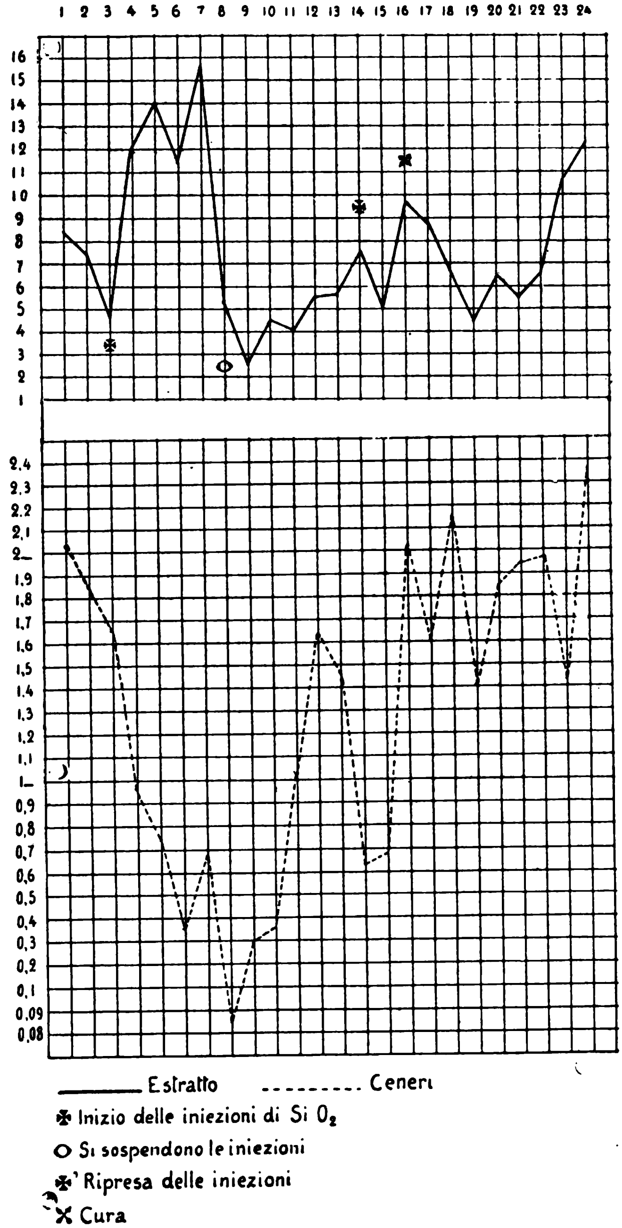


Fig. 17.


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
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0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,09
0,08
Estratto
Ceneri
Inizio delle iniezioni di SiO_2
Si sospendono le iniezioni
Ripresa delle iniezioni
Cura

Fig. 18.

lukemia and pernicious anemia, in which for an increase of chlorin there is a corresponding increase of phosforic residue. (8). We see on the other hand (Fig. 18) that the extractive substance proceeds in a sense inverse to the salts in the first, and then follows the same course to the end of the 2nd period. This fact signifies that to an offense to the organism due to the silica, there ensues a defense which tends to counterbalance the offense, that is the organism tends to neutralize the poison or the effects produced by the poison itself, without the assistance of mineral substances. This increase of organic substance causes us to think seriously that the silica is the cause of a destruction or of no small consumption of all the tissues with which it comes in contact.

And that in reality the silica is the cause of the anomaly, recognized in the composition of the urine of the dog in the experiment, we conclude from the analysis of the urine of the same dog for more consecutive days, during which no further injections of silica were made and which constituted the third period of the experiment. In this the quantity of urine saved was always low, with a mean of 83 c.c. in 48 hours and with a decreasing specific gravity, having fallen from 1.0468 to 1.0332.

At the same time, the fixed substance, in the total volume of urine in 48 hours, decreased from 11.700 to 4.980 and the ash increased from 0.568 to 0.902. Then, as the urine was approaching the normal composition and the ash was increased, the chlorin, the sulfuric residue, the phosforic residue and the alkalies were all more or less retained or less eliminated.

Most notable of all was the course of the sulfuric residue, which not only was increased in comparison to the ascertained mean of the 2nd period, but also was increased with respect to the 1st period or the normal. This fact demonstrates that the organism eliminates the accumulated sulfates and shows that the silica is the cause of no small dissolution of the sulfurous proteid substance of the tissues, since it is known that the surfuric residue of the urine "comes, for the greatest part, from the combustion of the sulfurous proteid substance of the tissues" (9). It demonstrates, also, that the silica fixes the proteid substance of the tissues themselves and causes them to be eliminated with a certain difficulty; since it was precisely in the period in which the injections were suspended, that we can see an increase of the combustion of the proteid substance of the tissues, an increase of the quantity of SO_4 eliminated, and a difference between the ash and the sum of the ions directly determined; or we see an augmentation of the defensive activity of the organism.

Tracing a curve with figures obtained in this period of the experiment (Fig. 16, 17 and 18) we see that the chlorin commenced to increase immediately, took a bound on the sixth day of the period, as the organism attempted to liberate the greater part of it fixed in excess, then fell, maintaining a height which was superior to the initial of the same period, showing that in time it might return to the normal if at all.

The sodium followed the same course as the chlorin and there is no doubt that it leaves the organism in the form ot the chlorid for the greater part. The curves of the phosforic residue, the sulfuric, the extract and the ash do not offer anything in particular, except a rather exaggerated emission which reveals an effort of the organism to get rid of the intoxicating material or to repair the waste produced by it and which it would yet produce by remaining in the tissues.

The 4th period comprehended 10 days of new injections of silica, made exclusively to see if the composition of the urine returned again to the values obtained in the second period, and if the silica were really the cause of the retention of the salts, as we had already seen.

In this period we have made only two analyses of the urine of 48 hours and of these one after 5 injections, one after 10. The results of the analyses were that the volume of the urine was always low, averaging 60; the specific gravity was increased from 1.0332, mean of the 3rd period, to 1.0546; the fixed substance was also increased from 4.980 to 7.395 in the mean of the total volume of urine of 48 hours and the chlorin decreased from 0.583 to 0.323. The surfuric residue was increased from 0.325 to 0.339; the phosforic residue from 0.369 to 0.823 and the alkalies fell from 0.266 to 0.185.

In the curves we have not seen that a depression rather marked was followed by an ascent, which was greatest in the phosfates; rather we have seen a period of retention which is followed by one of elimination. We come again to what we have seen in the 2nd period and because of which we *have no doubt that the silica in the animal organism works an accumulation of mineral substances and produces in consequence a destruction of the tissues.*

To the experiment, which we have just explained, because it has demonstrated the effect of silica almost pure in distilled water upon the animal organism, we have added another, in which, to a solution of silica a quantity of sodium chlorid was added corresponding to 0.5%. And this caused it to be observed that the chlorid of sodium added to the silica, modified its peculiar noxious action, rather than to establish the importance of the addition of chlorid of sodium to the ordinary ration.

The animal which has served for the experiment was a bitch instead of a dog, to avoid the loss of the urine, so easy with the male. The alimentation of the bitch was the same as that of the former dog; that is, bread and potable water, and the injections were made every day in the quantity of 3 c.c. of the double solution.

The results of the experiment are collected in the following table, divided into only two periods, one to establish the normal composition of the urine in captivity, the other to establish the composition of the urine under the influence of the substance injected.

In the urine of the second period indican was always found in small quantity except on the first days.

The figures of the mean in this experiment show that the volume of urine was increased in the 2nd period in comparison with the first period or the normal and that as a consequence the specific gravity was not distinctly diminished. And this is perhaps the only difference which distinguishes the action

TABLE 2a.

In One Liter of Urine.

Date 1913.	Volume of urine c. c.	Specific gravity	Fixed substance gm.	Ash gm.	Cl. gm.	SO$_4$. gm.	PO$_4$. gm.	Alkali Na. gm.
FIRST PERIOD								
Mar. 19.	200	1.0194	40.82	11.37	2.907	1.339	3.387	3.994
21.	140	1.0312	74.11	16.11	9.359	2.142	2.561	6.085
23.	164	1.0255	53.04	13.11	7.515	3.347	3.387	7.831
25.	140	1.0281	48.49	14.52	7.374	3.846	3.717	9.566
Mean	161	1.0260	54.11	13.77	6.788	2.668	3.263	6.869
SECOND PERIOD.								
28.	68	1.0329	58.98	17.925	5.672	2.446	4.956	4.411
30.	107	1.0279	46.57	14.090	5.317	2.374	3.882	4.092
Apr. 1.	344	1.0164	20.76	8.965	3,687	1.167	2.148	3.059
3.	220	1.0176	43.89	8.155	3.829	1.449	2.556	2.361
5.	176	1.0315	83.53	4.990	2.340	2.533	2.763	1.702
7.	110	1.0329	85.05	12.175	6.097	3.013	4.130	3.835
9.	295	1.0185	42.52	10.315	5.105	1.128	2.063	3.793
11.	180	1.0253	42.52	11.500	5.176	2.053	3.387	3.496
13.	215	1.0210	48.71	10.960	3.828	1.459	2.974	3.591
15.	140	1.0303	73.18	13.180	6.594	2.362	5.534	4.012
17.	260	1.0190	41.79	11.400	4.112	0.889	3.552	3.199
19.	225	1.0194	44.20	10.300	2.623	1.295	1.530	3.506
21.	185	1.0392	120.80	5.530	2.339	4.471	1.239	1.960
23.	175	1.0386	106.93	12.630	6.665	3.631	5.039	4.088
25.	145	1.0296	70.28	15.325	6.523	2.246	4.213	5.285
27.	170	1.0261	65.30	12.810	6.026	1.974	3.387	4.092
30.	205	1.0179	40.32	10.190	4.821	1.441	1.569	3.718
May 2.	300	1.0177	42.65	8.355	4.396	1.204	2.473	2.941
4.	240	1.0189	44.33	10.400	4.667	1.163	2.313	3.329
Mean	198	1.0253	59.01	11.008	4.727	2.015	3.142	3.498

of pure colloidal silica upon the animal organism from the action of the silica united with chlorid of sodium. Otherwise the action of both the solutions is almost identical; that is, an increase of the fixed substance, diminution of the ash, diminution of the chlorin, diminution of the sulfuric residue, distinct increase of the phosforic residue and diminution of the alkalies. We have said that the action was almost identical, because in reality the sulfuric residue was diminished and the phosforic residue increased, differing from what we have seen in the former experiment. All this induced in us the conviction that the chlorid of sodium modifies the action of the silica without antidoting it, that is, that the colloidal combination silica-chlorid of sodium is less violent than the silica alone, thus prolonging the appearance of its injurious effects. So true is this that the bitch killed after a period of 45 days of captivity and injections showed at the autopsy all the lesions pro-

In the Total Volume of Urine.

FIRST PERIOD.

Fixed substance gm.	Ash gm.	Cl. gm.	SO_4. gm.	PO_4. gm.	Alkali Na. gm.	Sum of the ions in the total volume	Difference between ash and the sum of the ions
8.164	2.274	0.581	0.268	0.677	0.799	2.325	—0.051
10.375	2.255	1.310	0.299	0.359	0.852	2.820	—0.565
8.698	2.150	1.232	0.549	0.555	1.284	3.620	—1.470
6.788	2.032	1.032	0.538	0.520	1.339	3.429	—1.397
8.506	2.177	1.038	0.413	0.527	1.068	3.048	—0.870
			SECOND PERIOD.				
4.011	1.218	0.385	0.166	0.337	0.299	1.187	—0.031
4.983	1.507	0.568	0.251	0.415	0.438	1.672	—0.165
7.141	3.083	1.268	0.401	0.739	1.052	3.460	—0.377
9.655	1.785	0.842	0.319	0.562	0.519	2.242	—0.457
14.701	0.878	0.408	0.446	0.486	0.300	1.640	—0.762
9.356	1.339	0.670	0.331	0.454	0.422	1.877	—0.538
12.543	3.043	1.505	0.332	0.608	1.118	3.563	—0.520
7.654	2.070	0.931	0.370	0.610	0.629	2.540	—0.470
10.473	2.356	0.823	0.313	0.639	0.772	2.547	—0.191
10.245	1.845	0.923	0.331	0.775	0.562	2.591	—0.746
10.865	2.964	1.069	0.231	0.924	0.831	3.055	—0.091
9.945	2.317	0.590	0.291	0.344	0.789	2.014	+0.303
22.348	1.023	0.433	0.827	0.229	0.363	1.852	—0.829
18.710	2.210	1.166	0.635	0.881	0.715	3.397	—1.187
10.291	2.222	0.946	0.326	0.610	0.766	2.648	—0.426
11.101	2.177	1.023	0.336	0.575	0.695	2.629	—0.452
8.265	2.089	0.988	0.295	0.321	0.762	2.366	—0.277
12.795	2.506	1.318	0.361	0.741	0.882	3.302	—0.796
10.639	2.496	1.020	0.279	0.555	0.799	2.653	—0.157
10.827	2.060	0.888	0.360	0.568	0.668	2.485	—0.459

duced by the silica alone in the other animals concerning which we have already given account.

If then with the figures reported in the table, we describe a curve as we have already done in the first experiment, we see again that the chlorin (Fig. 19), after the first injection, falls to the minimum, then rises to a maximum and establishes thereafter a periodic progress in which the amplitude of the oscillations is continually diminished until they approach, after 37 days, a straight line and remain thus to the end of the experiment, that is for 10 days more. The height at which the chlorin eliminated in the last period was maintained was a mean of 0.888, calculated from the total volume of the urine, a little less than the mean of the normal period 1.038, and still less than the mean of the normal period less the first determination really very low, 1.191. And if it is understood that this result is obtained by maintaining the bitch always in identical conditions of environment and alimentation and by always injecting the same solutions of silica and chlorid of sodium in equal measure, the spontaneous conclusion follows that under the action of these same injections, the elimination of chlorin is not only profoundly disturbed but tends, after crossing to a period of excess, to an equilibrium between the accumulation and elimination which we are constrained to call forced, since it is not concordant with the character of the organism. And the point of equilibrium, in fact, ought to be higher than the normal for the same animal, because the silica always maintains the cumulation of the salt, carried to the maximum, as its principal characteristic. There is no doubt, to establish this our affirmation, that the equilibrium returns or is not observed until it has returned to the normal equilibrium of the animal,

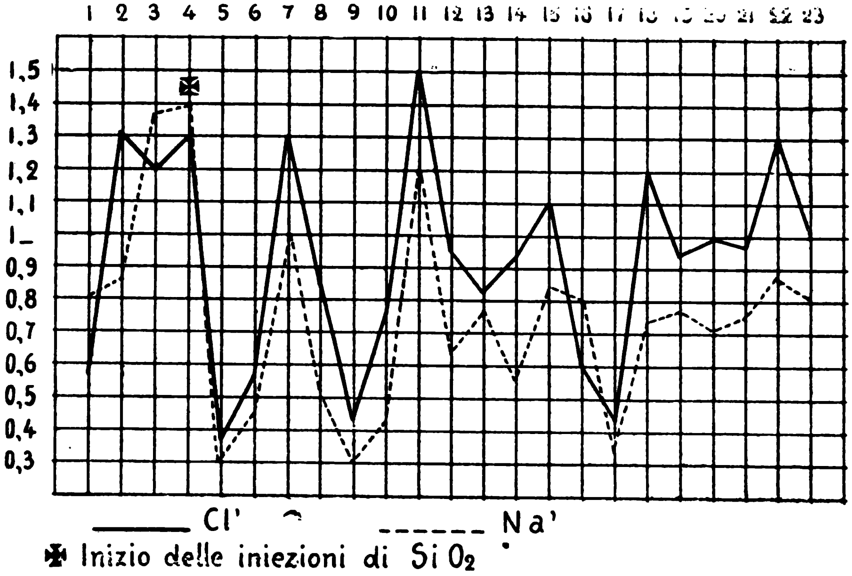

Fig. 19.

after a period of perturbation and discomfort. First, because the silica always acts by accumulating the chlorin, as is apparent from the mean, and by intoxicating the organism, as was shown at the autopsy of the bitch killed; second, because the quantity of chlorin introduced was always larger than that of the normal period; third, because it is incomprehensible that there should be an abnormal elimination without a previous accumulation; fourth, finally, because the elimination of chlorin in the pellagrous presents a similar physionomia; an elimination truly exaggerated and concerning which it was not possible to give a sufficient explanation. Because the experimenters necessarily avoided the period of accumulation or of the formation of the exaggerated equilibrium which we were able to show is one of fixation; therefore, the belief that pellagra was a disease characterized from the effects of the reaction, by a demineralization of the affected organism.

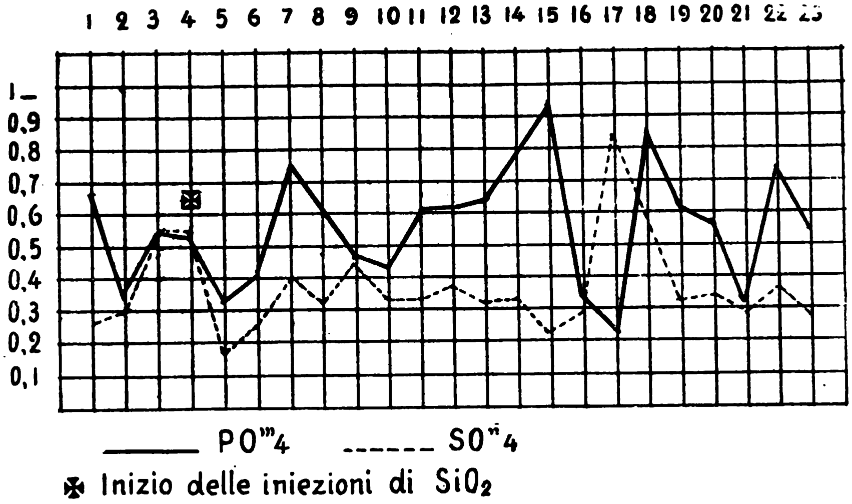

Fig. 20.

We have stated, just before, that an equilibrium is formed between the increase and elimination of chlorin not commensurate with the character of the animal organism, because, in reality, every individual of the same species has a point of equilibrium entirely its own and which depends upon the celerity, upon the intensity of the reactions which take place in the organism and upon all the internal and external conditions

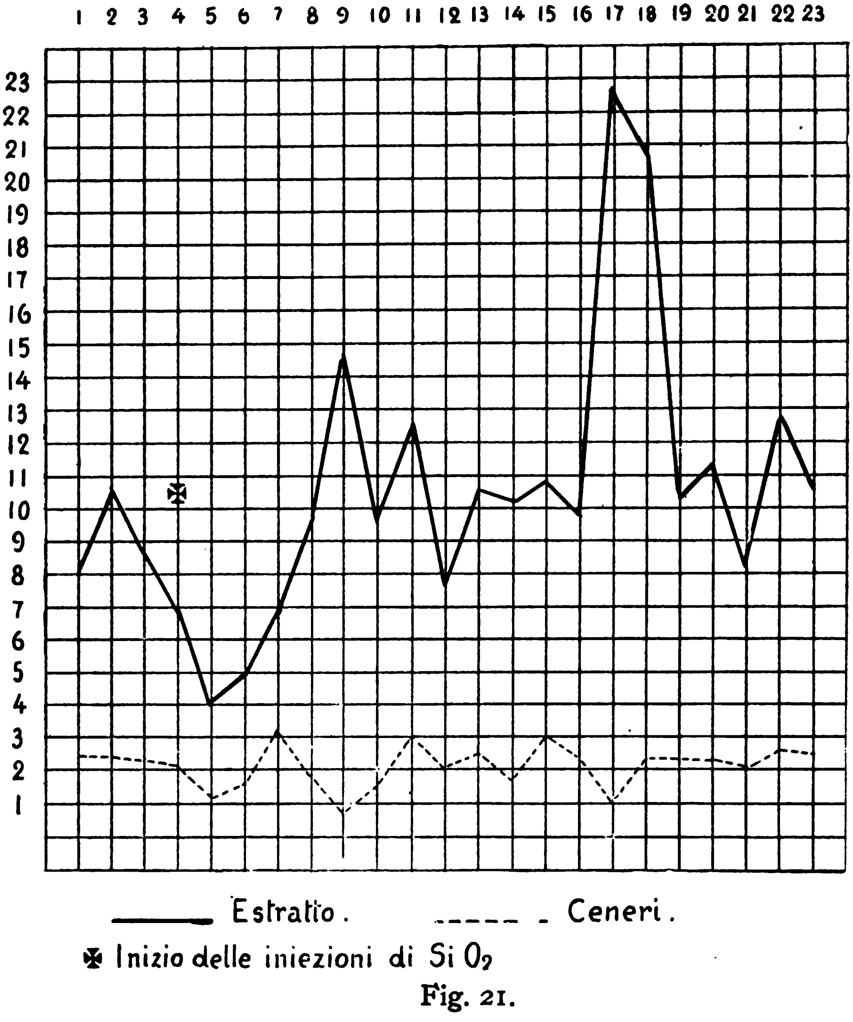

Fig. 21.

which are able to have any influence upon it. In fact, Girardi and Borelli (10), in a study of the reaction of sodium chlorid in healthy individuals, demonstrated the existence of "a personal coefficient of maximum elimination, with respect to a given quantity of chlorid of sodium introduced, which evidently exceeds the quantity habitually ingested." He evidently confounded with the elimination of chlorin in relation with the exaggerated quantity of chlorid of sodium contained not in the food, but retained in the organism by the action of the silica.

The same curve moreover demonstrates that the chlorin is eliminated in the form of alkaline chlorids, because it is in correspondence with very little divergence with that of the alkalies.

Then the curve of the phosforic residue (Fig. 20) corresponds with that of the chlorids; that is, when there is retention of one there is retention of the other, and vice versa. On the other hand the curve of the sulfuric residue very often has its maximum in correspondence to the minimum of chlorin and phosforic acid and vice versa; perhaps because the formation of sulfuric acid from the destruction of the tissues follows the maximum retention of the other salts and is independent of them.

This our supposition finds support in the fact that the period of maximum elimination of sulfuric residue corresponds in general to the period of maximum elimination of fixed substance (Fig. 21) and contemporaneously to a notable difference between the sum of the determined ions and the ash..

Finally it remains to understand the influence of alumina upon the progress of intoxication with silica; since we have admitted the possibility that alumina may be drunk especially in the form of an insoluble colloidal composition of silica-alumina or alumina-electrolyte, and which easily remains in suspension, communicating to the water a very distinct opalescence.

We have not been able in truth to make an experiment with the composition, silica-alumina, because we have not yet succeeded in readily preparing a large quantity of a colloidal solution of alumina and therefore we have used only a solution of silica in which we suspended a small quantity of gelatinous alumina, perfectly washed, insuring in this manner that the silica would remain in colloidal solution.

This suspension was injected in a dog, subjected to the same diet and to the same conditions as in the former experiments and of which we examined the urine of 48 hours. The results of the determinations are set out in the following table:

TABLE 3a.

In One Liter of Urine.

Date 1913.	Volume of urine c. c.	Specific gravity	Fixed substance gm.	Ash gm.	Cl. gm.	SO_4. gm.	PO_4. gm.	Alkali Na. gm.
May 11.	220	1.0202	47.03	8.050	2.482	2.094	3.717	2.802
14.	310	1.0215	46.28	9.200	3.970	1.678	2.478	3.016
Mean.	265	1.0208	46.65	8.625	3.226	1.886	3.097	2.909
May 16.	170	1.0217	47.75	8.400	3.190	1.599	4.130	2.705
18.	300	1.0256	68.02	8.425	4.892	2.535	3.139	2.922
22.	190	1.0271	70.01	12.095	6.381	2.388	3.634	4.288
24.	165	1.0307	72.83	13.950	7.161	2.615	3.056	4.870
26.	145	1.0361	92.75	16.815	6.523	2.872	5.699	3.640
28.	120	1.0348	91.83	14.315	5.885	3.109	6.295	4.458
30.	120	1.0350	89.12	16.515	5.885	2.355	4.873	4.830
June 1.	100	1.0305	76.55	12.040	2.694	2.625	4.295	2.828
3.	130	1.0329	84.95	13.410	5.247	3.336	5.369	3.821
5.	580	1.0307	71.72	19.900	9.784	5.186	1.487	6.827
7.	130	1.0399	105.91	16.060	6.806	3.589	6.112	4.496
9.	150	1.0354	96.30	10.900	5.956	3.258	5.699	2.646
11.	140	......	.....	......	5.672	.....	.....	.....
Mean	187	1.0317	80.64	13.568	5.852	2.939	4.482	4.026

The mean figures of this experiment show that under the action of the silica and alumina there was a diminution of the urine voided, an increase of the specific gravity and of the fixed substance as we have seen in the preceding experiments. They also show that the ash, the chlorin, the sulfuric residue, the phosforic residue and the alkalies are increased, differing from what we have seen in the preceding experiments.

Therefore, if with the figures of the various determinations we construct curves (Figs. 22, 23 and 24) we see that the chlorin, the sulfuric residue, the phosforic residue, the alkalies, the fixed substance and the ash, at the commencement of the injections, fell, rose again, thus beginning a periodic progress, which thereupon, with small oscillations resolved into a continuous fall until it reached a minimum on the 20th day of the experiment. On the 22nd day they manifested an elevation because on the 21st day the animal inadvertently escaped from the cage, ran around for some hours and drank profusely of potable water. Returned to the cage it voided in the night an extraordinary quantity of urine, because of which there was not only an unusual rise of ash but also of chlorin, sulfuric residue, phosforic residue and alkalies. Without this incident the mean would have had the same significance as in the preceding experiments. Under the action of the silica and the alumina there is retention of all the mineral substance determined except a slight difference which should either be ascribed to the alumina which accompanied the silica, or to the individuality concerning which we have already spoken. And hence we are able to say that the alumina has perhaps an action concurrent with that of the silica, or that the one and the other united have an action which is more energetic than that of the silica alone. The incident occuring, in every way seems to have served to demonstrate again

In the Total Volume of Urine.

Fixed substance gm.	Ash gm.	Cl. gm.	SO_4. gm.	PO_4. gm.	Alkali Na. gm.	Sum of ions in total volume	Difference between ash and sum of ions
10.347	1.771	0.546	0.460	0.817	0.616	2.439	—0.668
14.366	2.852	1.230	0.520	0.768	0.935	3.453	—0.601
12.356	2.311	0.888	0.490	0.792	0.775	2.946	—0.634
8.118	1.428	0.542	0.271	0.702	0.460	1.975	—0.557*
20.406	2.527	1.468	0.760	0.942	0.877	4.047	—1.520*
13.302	2.298	1.212	0.453	0.690	0.813	3.168	—0.870*
12.017	2.302	1.181	0.431	0.504	0.803	2.911	—0.617*
13.449	2.438	0.946	0.416	0.826	0.527	2.715	—0.277*
11.019	1.717	0.706	0.373	0.755	0.534	2.368	—0.651*
10.694	1.981	0.706	0.283	0.584	0.579	2.652	—0.671*
7.655	1.204	0.269	0.263	0.429	0.282	1.243	—0.039†
11.044	1.743	0.684	0.434	0.697	0.496	2.311	—0.568†
41.590	11.542	5.674	3.008	0.862	3.959	13.503	—1.961‡
13.768	2.088	0.885	0.466	0.794	0.584	2.729	—0.641
14.445	1.635	0.893	0.488	0.855	0.396	2.562	—0.927
......	.....	0.794	.....	.....	.....	.....	....
14.792	2.742	1.227	0.637	0.753	0.859	3.507	—0.775

*Albumin in the urine.
†No more albumin.
‡Released from cage the day before.

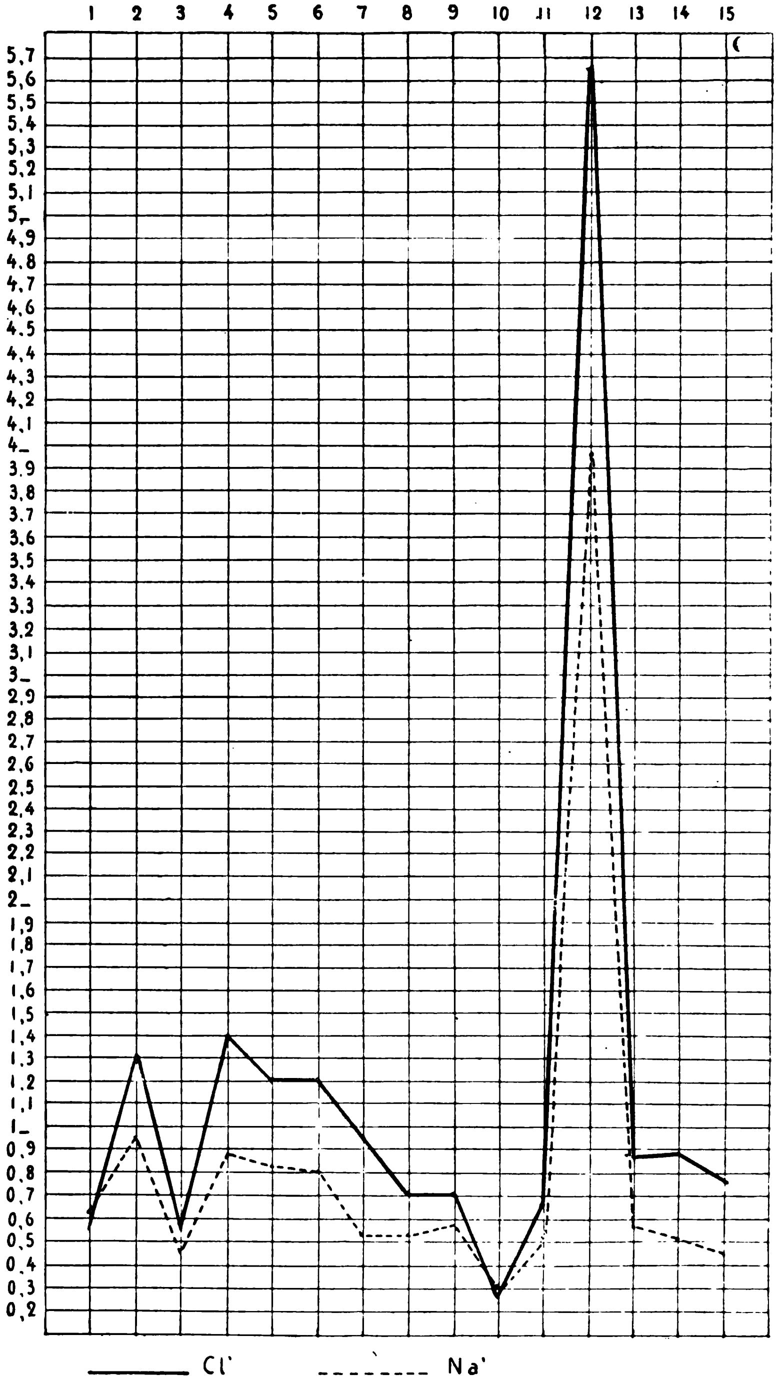
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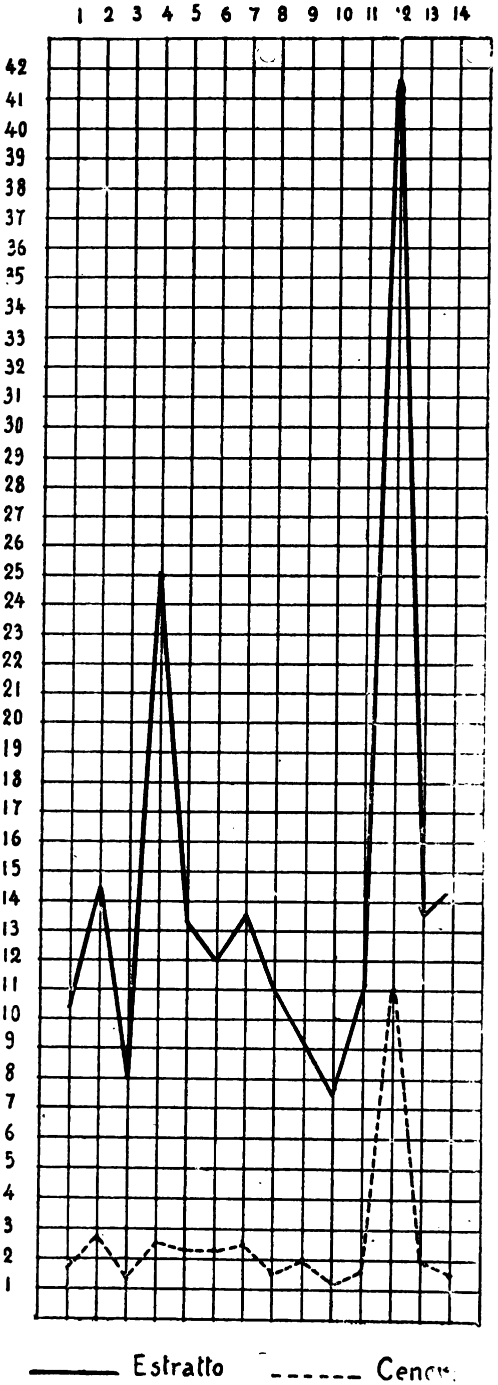
Fig. 22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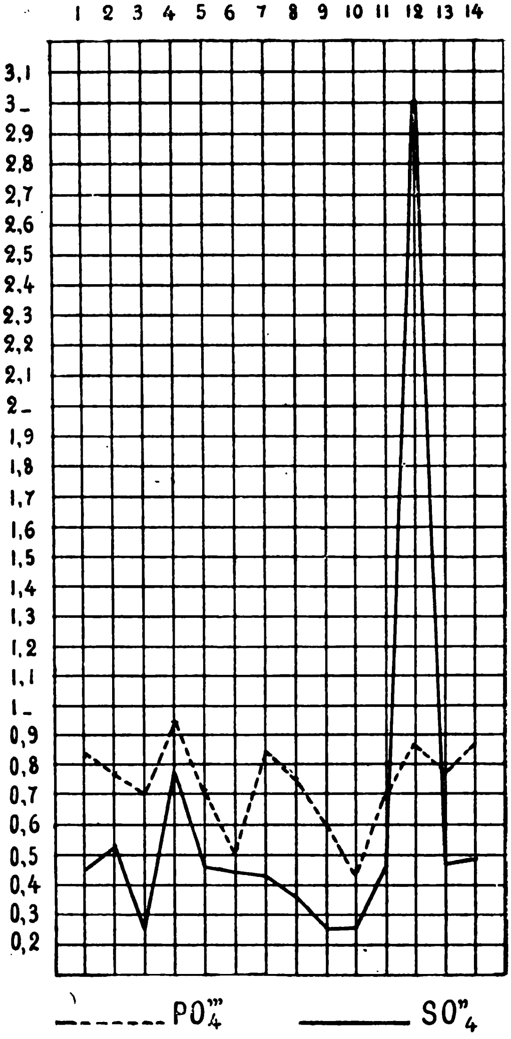
(Fig. 23)

the retention of salts taking place because of the silica or the silica and alumina, because it cannot be conceded that it does



(Fig. 24)

not or that it cannot be charged to this cause. And it serves also to demonstrate the importance that the change of the conditions of life have upon the change and hence upon modifications of certain states of the organism which receives benefit or injury from it. And we say change of the conditions of living, because the great voiding of mineral substances occurred not only from the water drunk, but also from the movement to which the dog was abandoned. In fact Borelli and Girardi have demonstrated by the abundant introduction of water, by itself alone, that a greater quantity of chlorin was not eliminated, but a lesser quantity, especially if the antecedent water diet was scarce.

On the 30th day the animal was killed and presented at the autopsy the characteristic signs of intoxication with silica, which we have fully discussed.

In the urine of the 2nd period indican was always found except on the first days.

DISCUSSION OF RESULTS.

The silica therefore, introduced into the animal organism, is the cause of retention of mineral salts, whether it is alone or united with chlorid of sodium or with alumina. And we are able to state, generalizing, that *silica is the cause of the retention of mineral salts in all living organisms and in all conditions;* because, according to Oberlin (11) the vine which grows in a silicious soil or in a soil treated wtih silicates, bears grapes richer in sugar than those which grow in a calcareous soil. And this occurs not only because the silicates influence the physical properties of the soil, especially its premeability, and its absorption of heat, and therefore a better nutrition of the vine and a better ripening of the grape, but also because the silica, having passed into the plant, is the cause of a chemical change. In fact, Hall, director of the Agricultural Experiment Station of Rothamstead, has established that the silicate of sodium, used as a fertilizer, has the effect of increasing the phosforus in the grain of the cereals, especially in barley, in which there is an acceleration of maturity. And it is not improbable that the need of silica felt by the oats to fructify and established by Haselhoff, is in relation with the need of phosfates for fructification, since they are accumulated by the silica. It is not improbable also that the silica acts analogously in the vine, accumulating phosforic acid, favoring the elaboration of sugar and modifying the composition of the must, so that it would yield a better wine, higher in alcohol and of better quality. And today there is no doubt that the fine wines always contain a greater quantity of phosforic acid that the ordinary wines (12).

At this time, whether the retention of the mineral salts and the beneficial or injurious effects derived from such retention are both due to the silica or the one depends upon the other, we are not able to discern with certainty. But, profiting by the facts already noted, we are able to make sufficiently clear the question which we have raised, by approximating the truth, even if we have not already arrived at the truth.

We believe that the retention of the salts is the first effect of the action of the silica, which, by combining by a colloidal reaction with a salt, transfers this same salt to the proteid substance. By a second colloidal reaction, the liberated silica, like diastase or the enzymes, makes a second really identical reaction. This finally produces a saturation of salts of the various tissues, compatible with all the conditions to which the organism is exposed or subjected and in obedience to the laws which regulate the equilibrium of these reactions. But if one of the conditions vary for any cause whatever, it is very easy to disarrange in organisms as complicated as ours, as in the lower animals and plants, the state of equilibrium modified in one sense or another; either toward a greater retention of salts or toward elimination. Whence, the periods of retention and elimination, without regularity in the same animal and the enormous elimination in the dog of the 3rd experiment above described, only because having escaped from the cage it drank and exercised, as it had not done while in captivity.

In order to write in formula the reaction which we have already indicated, it is necessary to recur to the hypothesis, stated by one of us (Scala) in collaboration with the lamented signora Mengarini (13) in which it was supposed that the particles of matter, passing into colloidal solution, resulted from a combination of the matter itself with a number not yet definable, of molecules of water separated into their respective ions. Therefore the mixture or the particles in colloidal solution would have the form expressed by one of the two following formulae:

$$P_m(\overset{-}{OH}{}'\overset{+}{H}{}')_n \qquad P_m(\overset{+}{H}{}'\overset{-}{OH}{}')_n$$

in which Pm indicates the colloidal mixture. Therefore the material dispersed in this manner in the water may be a hydrate of hydrogen or a hydrogen hydrate, as the material itself disposes of its force so as to attract to itself one rather than the other of the ions of the water and then as to its own quality.

The electrolytes, coming in contact with the material in colloidal solution combine with it by substituting a greater or less number of the ions of the water. The one or the other:

$$P_m(\overset{-}{OH}{}'\overset{+}{H}{}')_n + NaCl \rightleftharpoons P_m{}^{\overset{-}{Cl}{}'\overset{+}{Na}}_{(\overset{-}{OH}{}'\overset{+}{H}{}')_{n-1}} + H_2O$$

$$P_m(\overset{-}{OH}{}'\overset{+}{H}{}')_n + (NaCl)_n \rightleftharpoons P_m(\overset{-}{Cl}{}'\overset{+}{Na})_n + nH_2O$$

And since it is known that colloidal silica absorbs or fixes the alkalies with great affinity and the strong acids with much less affinity (14), it is supposed that it would have next to itself the oxyhydril rather than the hydrogen, assuming the properties of a hydrate of hydrogen. This, by contact with the electrolytic salt is changed in the manner expressed in the general formula stated above, forming compounds near the minimum or near the maximum, principally according to the concentration, the degree of dissociation of the electrolyte, the temperature and the force with which the salt combines with the mixture.

And that colloidal silica absorbs from solutions the chlorids, the sulfates and the nitrates of sodium and potassium is known through many experiments and it is also known that vegetable mould, washed with hydrochloric acid in ebullition, still absorbs through the silica which it contains, the phosfates, the carbonates and the alkaline borates (15). Moreover, Meyer (16) has observed that the *sol* silica acid passes in considerable amount through a dialyzing membrance when it is united with chlorid of sodium, because it forms a combination which is nearer the state of a true solution or to the state of molecular dispersion; or that the colloid, neutralized by the chlorid of sodium, has lost the power of adhering or of labile combination with the material of which the dialyzing membrane is formed. And we have said neutralized, referring to the electrical character: because Burton (17) has demonstrated that the concentration of the electrolytes in *sol* being augmented by degrees, the celerity of kataphoretic translocation of the mixture assumes values continually smaller until they arrive at neutrality and a change of direction follows. This signifies that the double electric character with which the colloid is furnished, is first neutralized by the double electric character of the molecule of the salt split into ions, to which succeeds a deaquification which is always more complete with the inclusion of the saline ions in increasing concentration.

There is no doubt then that the colloid silica combines with a certain avidity, the alkaline salts, and that it has the power to accumulate as we have stated elsewhere, either outside of living organisms or after it has penetrated their tissues.

And here we assume a diastasic or enzymatic function by which the salt, fixed by the colloid, is transferred to the proteid substance of the tissues themselves, either because it is abundantly accumulated by the colloid or through a very high grade of combination attained by the colloid itself, or through an affinity of the salts of the organic colloids superior to that of the silica colloid, or also through an intermediate substance which frequently functions as an excitant or determinant of such reactions. And it is through this that the colloidal silica fixes an abnormal quantity of salts in the tissues and maintains it there in the same quantity until it is present in excess of the physiologic. And when, for any cause whatsoever, the tissues are liberated from the excess of salts the silica recharges them.

We are able to represent this action with the following formulae:

$$[SiO_3H_2]_m(\overset{-}{O}H'\overset{+}{H}')_n + (NaCl)_n \rightleftharpoons [SiO_3H_2]_m(\overset{-}{Cl}'\overset{+}{N}\acute{a})_n + nH_2O$$

$$[SiO_3H_2]_m(\overset{-}{Cl}'\overset{+}{N}\acute{a})_n + P_m(\overset{-}{O}H'\overset{+}{H}')_n \longrightarrow$$

$$[SiO_3H_2]_m(\overset{-}{O}H'\overset{+}{H}')_n + P_m(\overset{-}{Cl}'\overset{+}{N}\acute{a})_n$$

In these formulae, in which Pm indicates a mixture of proteid substance, it is clearly seen that the colloidal silica, as it enters the reactions, is freed again at the end of the reactions. To a degree therefore, it can continue this same action indefinitely, in the same manner as diastase, as long as the silica remains in the tissues and as long as secondary actions do not interfere.

Wherefore, it should be of very great interest to know if the silica remains for a long time in the tissues or accumulates in them. Because a long permanence or an accumulation would be significant that between the colloidal silica and the proteid substance of the tissues there was a great affinity of combination and that an elimination was not possible, except by resorting to special measures and also at obscure times. But a direct solution of this problem is not possible for us, through the lack of a large platinum crucible, in which we could accomplish the destruction of the organic matter, because glass and porcelain always yield silica.

Nevertheless, it is possible to hazard one foresight, profiting by the determinations made by Bieler-Chatelan (18) upon grain coming from silicious soils and upon those coming from marl soils, since they have said, if the silica is a direct factor in the increase of sugar, it ought to be found in a larger quantity in the grain coming from silicious soils and less in that coming from calcareous or silico-calcareous soils. The experiment gave the following results:

Grain of Chamblandes (silicious soil) SiO_2 per Kg. 0.023,

Grain of Chavorney (marl soil) SiO_2 per Kg. 0.022, or, the same quantity in both.

Then, the silica does not accumulate in the vegetable organism, so it is not probable that it accumulates in the animal organism. This causes us to believe that having penetrated the living organism, it is eliminated after it has exerted its action, and is replaced by other furnished by potable water and food to continue the action left interrupted by the preceding.

This induces in us the conviction that the silica acts indirectly and in the same manner in the animal organism as in the vegetable organism and that there are conditions through which the silica is able, also in the vegetables, to show its action freely and without obstacles, and conditions by which the same action is modified or even neutralized; otherwise it is not comprehensible how an equal quantity of silica can correspond with effects so different. Also in the vegetables, it is not improbable that the carbonate of calcium exhibits the same neutralizing action which we have already established in the animals, since in the marl, the carbonate of calcium antagonizes the silicate of alumina found in considerable amount.

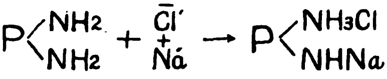
Therefore, it seems to us without doubt that the silica fixes the mineral salts in the proteid substance of the tissues with a continuous incessant action, which may be confounded with an enzymatic or diastasic action.

In what manner, therefore, an abnormal fixation of salt in the proteid substance of the tissues is able to produce such injurious effects as we have established and described in the animals can not be comprehended and as much less explained, if it is not admitted that from the fixation of the salt other reactions have their origin, to which, up to this time, we have given too little attention.

In fact, in 1906, one of us (Scala) in collaboration with Mengarini (19) demonstrated that the red corpuscles of the blood and the Opaline, small unicellular beings, without mouth, living in the cloaca of the frog, were markedly altered and died in an isotonic solution of chlorid of sodium in distilled water. This action could not be attributed to altered pressure or to an unfavorable physical condition other than that the chlorid of sodium had penetrated the interior of the red corpuscles or the body of the Opaline. So much so that this noxious action could be absolutely counteracted whenever the isotonic solution was prepared, instead of with distilled water, with a potable water containing other salts in solution, among them the earthly carbonates and the alkaline carbonates.

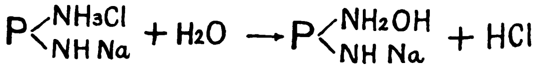
In a later communication one of us (Scala), still in collaboration with Mengarini (20), placed in evidence the impossibility of generalization of the supposition of Loeb, that the effects corrective of the injurious action of chlorid of sodium were due simply to the bivalent kations, and demonstrated corrective action was produced not only by the carbonate of calcium, but also by the alkaline carbonates in general, which contain a monovalent kation. For this reason it becomes necessary to suppose that the chlorid of sodium, coming in contact with the protoplasmic substance, combines with it and from the combination free hydrochloric acid results, very inconvenient to the life of the cell and to the being experimented upon, and which can be readily neutralized by any alkali whatsoever.

Still, if with this the fact is explained, in a rough manner, it is not explained by what reaction or successions of reactions hydrochloric acid should be liberated from chlorid of sodium by coming in contact with the proteid substance of protoplasm. Indeed no thought has been given to a reaction between the lateral amino-groups, which are found in the proteid molecule, and the mineral salts (21). In such a case the combination can be represented with the following formula:



$$P\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix} + \begin{matrix}\bar{Cl}'\\ +\\ \dot{Na}\end{matrix} \rightarrow P\begin{matrix}\diagup NH_3Cl\\ \diagdown NHNa\end{matrix}$$

This clearly gives a reason for the facts observed and reported, because the sodium-acid proteid has the power to liberate hydrochloric acid by hydrolysis as the following formula indicates:



$$P\genfrac{}{}{0pt}{}{\diagup NH_3Cl}{\diagdown NH\,Na} + H_2O \longrightarrow P\genfrac{}{}{0pt}{}{\diagup NH_2OH}{\diagdown NH\,Na} + HCl$$

And the acid liberated has the power to unite with sodium again to form salt whenever its concentration in the liquid shall have reached or passed a determinate limit, since the chlorin and the sodium in the proteid combination are independent of each other and hence are eliminated separately, according to their degree of dissociation and hydrolization. Of this we have a proof in an insoluble compound which we have obtained by treating solutions of egg albumin with concentrated solutions of sulfate of copper. This compound always contained an amount of SO_4 less than was necessary to form neutral sulfate of copper with the Cu already existing in the compound, and on the other hand, the water in which the above mentioned compound was formed, contained an amount of SO_4 which was greater than was necessary to transform the Cu into neutral sulfate (22). Moreover, by prolonged washing of the insoluble compound, the sulfuric residue, SO_4, and the copper are never eliminated in the precise amount to form neutral sulfate, but always with an excess of the first over the second, so that it arrives at a moment in which it no longer exists in the washed SO_4 compound of the precipitating salt and only as Cu (23).

Therefore, conditions exist in these compounds of proteid substance with neutral salt, by which the acid of the salt which enters into the combination is set free, because there is a tendency in these same compounds to pass from metallo-acid-proteids to metallo-proteids.

This manner of interpreting the facts observed in the red corpuscles and in the Opaline presents a very high degree of probability while it remains in the group of proteid substance, in the molecule of which we have reason to believe the lateral amino-group exists. But although we see the same facts and the same reactions in the mineral colloids in which the existence of an amino-group is not supposable, we have acquired the conviction that the reaction is more general and that it is closely connected with the colloidal state.

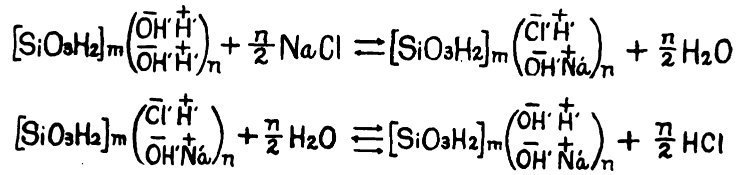
In fact, Linder and Picton (24), by coagulating the sulfid of colloidal arsenic with chlorid of barium, observed that one part of the precipitating salt was decomposed and that the barium of this part remained in the coagulum in spite of very prolonged washing, and that it set free a corresponding quantity of hydrochloric acid.

Hardy also (25), by treating suspensions of cement with different quantities of electrolytes, to determine the least precipitating quantity of the latter, has established that the precipitate always contains the metal of the precipitating salt and that the liquid has an acid reaction.

Morawitz, (26) also, in studying the superficial absorption of carbon by the sulfate and acetate of silver has seen that the deportment of one is very different from that of the other, concluding that the carbon has in the one a strong chemical influence since in a moment it rapidly decomposes the acetate of silver with liberation of acetic acid.

And, moreover, if it is admitted that in the precipitation of the colloids by means of the neutral salts, there is an accumulation on the surface of the mixture of either the anions or the kations, it is admitted also implicitly that the surrounding liquid acquires a reaction either alkaline or acid by hydrolysis of the part not absorbed.

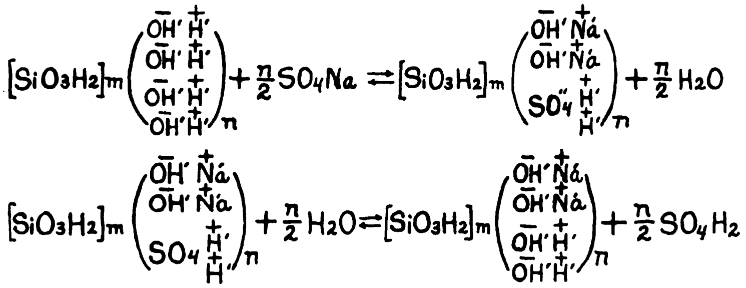
Therefore, rather than to a particular reaction, we have come to a reaction, if not general, common to a group of colloids in which the difference can be only of degree. And the formation of the surrounding acid or rather the formation of free acid in the reaction between the colloids and the salts, is explained in the same manner and equally well as in the case of the existence of the lateral amino-groups, being the substitution of the ions of water in the mixture. Hence the reactions can be represented by the following formulae:



$$[\mathrm{SiO_3H_2}]_m\begin{pmatrix}\overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{H}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{H}}{}'\end{pmatrix}_n+\frac{n}{2}\mathrm{NaCl}\rightleftarrows[\mathrm{SiO_3H_2}]_m\begin{pmatrix}\overset{-}{\mathrm{Cl}}{}'\,\overset{+}{\mathrm{H}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{Na}}{}'\end{pmatrix}_n+\frac{n}{2}\mathrm{H_2O}$$

$$[\mathrm{SiO_3H_2}]_m\begin{pmatrix}\overset{-}{\mathrm{Cl}}{}'\,\overset{+}{\mathrm{H}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{Na}}{}'\end{pmatrix}_n+\frac{n}{2}\mathrm{H_2O}\rightleftarrows[\mathrm{SiO_3H_2}]_m\begin{pmatrix}\overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{H}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{Na}}{}'\end{pmatrix}_n+\frac{n}{2}\mathrm{HCl}$$

And if, instead of chlorid of sodium, sulfate of sodium enters into the reaction, the reaction has a progress similar to the preceding:



$$[\mathrm{SiO_3H_2}]_m\begin{pmatrix}\overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{H}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{H}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{H}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{H}}{}'\end{pmatrix}_n+\frac{n}{2}\mathrm{SO_4Na}\rightleftarrows[\mathrm{SiO_3H_2}]_m\begin{pmatrix}\overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{Na}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{Na}}{}' \\ \mathrm{SO_4}''\,\overset{+}{\mathrm{H}}{}' \\ \overset{+}{\mathrm{H}}{}'\end{pmatrix}_n+\frac{n}{2}\mathrm{H_2O}$$

$$[\mathrm{SiO_3H_2}]_m\begin{pmatrix}\overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{Na}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{Na}}{}' \\ \mathrm{SO_4}\,\overset{+}{\mathrm{H}}{}' \\ \overset{+}{\mathrm{H}}{}'\end{pmatrix}_n+\frac{n}{2}\mathrm{H_2O}\rightleftarrows[\mathrm{SiO_3H_2}]_m\begin{pmatrix}\overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{Na}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{Na}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{H}}{}' \\ \overset{-}{\mathrm{OH}}{}'\,\overset{+}{\mathrm{H}}{}'\end{pmatrix}_n+\frac{n}{2}\mathrm{SO_4H_2}$$

And now it seems to us that through chemical proof and scientific deductions, it is no longer possible to doubt that in certain reactions between colloids and salts, the acid is set free which in the salt was bound to the base. And to fortify us in this state of mind comes the biochemic proof given by one of us (Scala) in collaboration with Mengarini. In this the Opaline, immersed in an isotonic solution of saccharose containing methyl violet was colored while living a distinct violet throughout, while the Opaline and the Paramecium, in isotonic solutions of sodium chlorid also containing methyl violet were colored while living a decisive azure. So also the cells of Spirogira, altered by immersion in a 3% solution of sodium chlorid containing methyl violet were colored azure, while those not so altered were colored violet (27).

With this knowledge, therefore, it does not seem difficult to understand the mechanism by which the silica intoxicates the living animal organism and by which it stores the saccharine material in the grape.

Because the proteid substances of the tissues, charged with mineral salts tolerate as we have already seen, and set free an amount of acid which is certainly greater than that which they would set free under normal or physiological conditions of the organism, it is not possible to exclude that an exaggerated fixation of salts corresponds relatively to an exaggerated liberation of acid.

The abundant and insistent mineral acidity through the continued action of the silica, disturbs the functions of the entire organism or of the separate organs more or less, according to the resistance of the individual and of the separate tissues and according to the means of defense more or less potent which they are able to activate. And it is precisely through action and reaction that the tissues wear out and waste and increase in the urine the organic products of regression, as if the whole organism were subjected to an uncommon activity or labor.

It is not necessary that the excess of acidity of which we have spoken should be great: first, because the disturbances which the silica causes have a character distinctly chronic, or are the result of slight and continuous action; further, because the acidity is due, not to one acid alone, but to a mixture of three: hydrochloric, sulfuric and phosforic, the chlorids, sulfates and phosfates being fixed or retained, although not in identical proportions. And we know that the deleterious action of these acids increases in the order in which these same acids have been written and that rather remarkable effects may correspond to a slight acidity, especially because of sulfuric and phosforic acids.

Indeed, it seems to us that the explanation of the increase of sugar in the grape is not difficult, because of the incompetence of the vegetable physiology. Since to an acidity exceeding the normal there is a corresponding or a great activity in the whole vine and hence also a greater and a better fructification; or there is a more active corresponding transformation of the hydrates of carbon in certain parts of the vine itself into the sugar of the grape. Also they, as in the animals, do not have a deviation of a determinate function, but simply an exaggeration, to which corresponds an exaggeration of the effects of the same function, until sometimes it becomes pathologic.

We have already examined the results of not a few analyses of the urine of pellagrins and are suddenly struck by the truly large amount of mineral substances contained, among which the chlorid of sodium predominates, by the small quantity of urine passed in 24 hours and by the presence of indican. We have examined the rest of the mineral substance in the pellagrous and are again struck by the exaggerated loss of all or almost all of the mineral substances, among which also the chlorid of sodium predominates. It is notable also that the loss of mineral substance in the pellagrous is relatively more through the feces than through the urine, except in chlorid of sodium; contrary to that which occurs in a healthy person.

All this is in plain contrast with the results obtained by us in the animals subjected to the action of silica, at least with regard to the urine, because we have always observed a retention of salts alternated by a period of elimination. Hence, it is said that silica is not the cause of pellagra; therefore, before coming to this conclusion it is necessary that we examine well into the results of the experiment to determine its true significance.

. We recall again distinctly that the results of the analyses of the urine of the animals in the experiment refer to the initial effects of the silica, either administered alone or in combination with other substances; while the results of the analyses of the urine and the feces of pellagrins refer to a very advanced stage of the action of an intoxicating substance which could be silica. Whence the diversity of the two products of an excretion very important to the organism.

Therefore, if we record the analytic data which refers to the bitch into which silica and chlorid of sodium were injected at the same time, and if we record also the reasons given for them, we see that the divergence is not as great as it appears. Because in the bitch there is clearly seen a tendency to the formation of an equilibrium between the fixation and elimination of salts which is not common and physiological in the animal, but an equilibrium the point of which is placed high because of the silica, and which we are able also to call pathological. And it is because of this that to a greater fixation of salts to which the organism becomes habituated, there follows a greater elimination which is the normal elimination of the pathological state of the diseased organism.

A pellagrin, when he came to our notice and was examined, was found to be exactly in this second period, which is also the period of morbose manifestations, in which a pathological equilibrium is formed and, therefore, with it an exaggerated elimination of chlorid of sodium. Undoubtedly the period of retention or of preparation had passed, because no one yet suspected that a person who did not complain of speecific disturbances and had no objective and characteristic signs could be a pellagrin in the beginning of his sickness or of the intoxication. And so because the period of retention of mineral salts, admitting always that the cause of pellagra is silica, passes and disappears entirely, it is not even suspected by anyone. It is an inaccuracy, therefore, to qualify the organism of the pellagrin as demineralized or as in the course of demineralization, because, in a true demineralization, other signs should be manifested and perhaps differing from those characteristic of pellagra and because demineralized should be applied to those organisms which are not in the best condition and which always and constantly eliminate mineral substance in an amount greater than the normal. We believe, in every case that in differing organisms the point of equilibrium between the absorption and elimination of salts is different; because in every one the functioning differs as to quality and quantity, although similar. And we believe Borelli and Girardi, already cited, desired to allude to this when they stated that "there exists a *personal* coefficient of maximum elimination of chlorid of sodium with respect to a given quantity introduced, since it evidently exceeds the amount habitually ingested." To us this also shows that the proclivity of retention differs from organism to organism, or that the charge of salt differs in different organisms. These deductions have a very great importance in the pathogenesis of all the diseases of change and especially of pellagra, because we may arrive at an explanation of what is in this case at least, the *individual coefficient,* how much it concurs in the attack, in the manifestation and in the course of the disease. Because if, in reality, pellagra is a disease consequent upon a forced accumulation of salt, as does not appear doubtful, pellagrins ought to be those individuals whose organisms have a proclivity to the retention of salts, or to the formation of an equilibrium between fixation and elimination, of which the point is higher and near the point of pathological equilibrium. On the contrary, pellagrins should not be of those organisms without a proclivity to retention, nor of a proclivity to exaggerated elimination, or in which the point of equilibrium is very low and in which no forced accumulation is able to arrive at the point of pathological equilibrium. Between these two extremes are placed all the cases with a tendency to one or the other, or with a tendency to become easily pellagrous or to resist easily, separating naturally from a common point, which may be called neutral.

And it is this that explains the fact which has impressed and still impresses all, that is in one family, the members of which are subject to the same conditions of life, of environment, less perhaps of labor, the sick of pellagra are one or possible two; because these are predisposed or because they had acquired a predisposition through circumstances which it is not possible to define a priori, but which in one way or another can be determined. Thus for example, it is noted that pregnancy, strong impressions and accidental cold baths predispose to pellagra, because all are causes which modify the chemistry of the entire organism and perhaps modify the change of the mineral salts.

This explains also why our experimental animals, which were subjected to the same conditions of life and received the same amount of silica, died at such very different times: one rabbit lived 214 days, having received 107 intraperitoneal injections. .

All this agrees wonderfully with what Devoto and De Giovanni thought and wrote. Because, according to the one, "pellagra may become evident and extrinsic when an accidental disease breaks out or a great moral breakdown, which interrupts that complex of circumstances which pertain to the individual, as a glimmer of balanced resistence" (29); according to the other "the study of the external causes of pellagra should not be separated from that of the internal and predisposing causes; pellagra attacks through this and according to the receptivity of the individual" (30).

Therefore, concluding, we are able to state that pellagra is a disease caused by forced retention of mineral salts, to which succeeds an excessive liberation of acids, with respect to what is considered as normal for the determinate organism, or pellagra is none other than a mineral acidosis with all its consequences.

To this same conclusion Moreschi arrived (31), by analyzing the urine of the pellagrous, in the nitrate part of which he found notable amounts of ammonia and of carbamic acid, always greater than that found in the urine of non-pellagrous persons. That is, while in the one the mean amount of ammonia nitrogen, including that of the carbamic acid, is 8.50% of the nitrogen eliminated, and in the other is about 13.5%. Therefore, "the disturbance of nitrogenous change in the pellagrous is distinctly explained with ammonuria, which is in very close *relation with an acid intoxication*" ammonuria which we have only suspected in our animals, since the difference between the sum of the determinate ions and the ash was almost always more notable in relation to the greater amount of extractive substance or when the tissues were found in a greater pathological activity and hence in greater destruction and greater consumption. And indeed, the effort to which the organism is subjected to be freed of the deleterious substances, which are the mineral acids, may be precisely the elaboration of an alkali for neutralization, and the alkali in this case can not be other than ammonia which should be derived from the degradation of the proteid substance.

At this point we should inquire if the exaggerated fixation of the mineral salts occurs always and exclusively under the action of silica which continually enters and which is continually eliminated; or through a new capacity or habit acquired by the tissues.

By examining the results of the experiment with dog No. 11 (Tab. 1 and Fig. No. 16, 17, 18), we see in reality that the injections of silica being suspended, the urine almost returned to the normal after 10 days, but still remained high in specific gravity and in extractive substance. And this seems to us the same that occurred in the pellagrous, removed from their environment, since the substance eliminated by the urine was almost normal if the chlorin be excepted which was in reality somewhat higher, taking into account the marked dilution of the urine (see the following table) (1).

Then the silica also in the pellagrins should be eliminated and presumably is eliminated (32) through the urine or through the feces; since the cumulative action of the mineral salts and the effect of this same action is slightly diminished. And if this is so, and if, on the other hand, the effects of the silica remain long, we must admit that a prolonged action of the silica, as we have in the pellagrous, produces its own true weakening of the powers of combination, with the salts, of the material of the tissues or else a new habit, without weakening at the same time in equal measure the reactions of compensation. And that the animal organism yields to these deviations, it puts in evidence the fact that for an animal it may be curative or it may be reactive in full efficiency, even after the cessation of the injections of the substance by which the specific reaction is obtained, for a considerable time.

From this it is deduced that pellagra is a disease which is

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(1) The analyses which are reported pertain to the urine of two advanced pellagrins at the Pellagrosario Umbro of the City of Castello, directed by Dr. Fortunato Fabbri.

TABLE 4a.

Date. Feb. 1913.	Sp. gr. at 15°	Residue. % gm.	Cl. % gm.	SO_4. % gm.	PO_4. % gm.	Na. % gm.	Ash. % gm.	Sum of ions in total volume.	Difference between ash and sum of ions.	Cl. 100 residue.
				Rosa Valentini.						
7.	1.0083	13.85	6.850	4.431	0.463	0.552	2.648	8.094	—1.244	31.99
12.	1.0071	15.72	5.725	2.977	0.761	0.878	2.078	4.616	+1.109	18.93
14.	1.0118	19.98	9.260	5.246	0.761	1.438	2.322	9.767	—0.507	26.25
16.	1.0119	24.78	8.465	4.041	1.127	4.213	2.607	12.088	—3.623	16.30
21.	1.0120	23.01	4.700	0.851	1.286	2.763	1.771	6.671	—1.971	3.09
Mean	1.0102	19.47	7.000	3.509	0.879	1.969	2.285	8.247	—1.247	19.43
				Domenica Sarti.						
7.	1.0180	37.17	9.440	3.545	1.945	4.199	2.995	12.644	—3.204	9.53
12.	1.0115	22.00	10.160	5.530	0.565	.....	3.591	......	....	25.13
16.	1.0164	32.07	12.700	6.948	1.303	2.430	4.499	15.180	—2.480	21.66
Mean	1.0153	30.41	10.766	5.341	1.271	3.314	3.681	13.912	—2.842	18.77
				Normal Figures.						
	......	.....	......	2.283	3 354	2.750	3.035	......	....	.....

difficult of cure with hygienic treatment, but it simply mitigates the severity and does not avoid the recurrence in the spring and summer. For a true cure there is necessary the continuous and prolonged action of a substance which modifies the pathological condition of the tissues and returns them to a normality proper to the organism, when the mineral acidity naturally has not caused alterations such as are no longer controvertible.

Finally we will attempt to explain the epidemiological fact, which Gosio qualifies as "a phenomenon circumscribed by time," and precisely between March and April, when "the endemic arouses to assume the character of a true paroxysm" (33).

On the whole, it does not seem to us that pellagra is a disease determined by season because in that season one determinate symptom is more apparent, more impressive and more characteristic, that is the cutaneous eruption. But pellagra is a disease of all the months of the year and the vernal endemic paroxysm is the same as in the winter, since the number of pellagrins in the winter is the same as those coming over from the spring, increased by new patients becoming sick and diminished by those passed to a better life. In fact, if pellagra is a disease of chronic intoxication, its manifestations would not be so rapid as from winter to spring except in a case of exceptional violence (34). And if it is a disease which is cured with difficulty, it would not disappear in the brief time from spring to the first months of summer in which there is a disappearance of the cutaneous erythema. And this is so true that in the spring to come there will be the same pellagrins of the year before, who have the same manifestations, who receive the same help accorded by the special law, increased as we have stated by the newly sick or diminished by some others.

Therefore, there is a determinate time between the manifestations of pellagra, which can be explained by the intoxication with silica. Because in the winter the acid intoxication is increased in the tissues and is tolerated without disturbance by the aid of the low temperature and the vegetative quiet of the entire organism. And the suppressed function of the sweat and the diminished eliminative functions especially contribute to this acid concentration. At the beginning of spring the accumulated acids irritate in relation to the increase of temperature, the old tissues and still more the new tissues which had been forming in this period of repressed vital activity. Hence the cutaneous erythema on the points exposed to the sun and at any time greater heated, the return of the intestinal disturbances and the accentuation of the nervous disturbances. With the arrival of summer and the increase of temperature the cutaneous disturbances cease because of the diminution of the acid concentration through the increase of elimination by sweat and through other channels, through a greater resistance acquired by the new tissues becoming adult and also through neutralizing substances which are able to be introduced in greater abundance with the food and with the drink.

And we have found a confirmation of this our explanation in a case referred to by Tiles (35), which we relate here.

A pellagrous woman, who did not yet have any sign of erythema, was constrained to work in the kitchen to prepare a meal in the temporary absence of the cook. The next day she had an acute erythema of the face and hands of which the determining cause was undoubtedly the high temperature of the kitchen. This fact casts serious doubt upon the action of the luminous rays of the sun, as the cause of the erythema and confirms our idea that they act because they are accompanied by calorific rays.

Therefore the endemic paroxysm does not exist except in the periodic manifestation of one of the symptoms more apparent and not the only one of the intoxication to which has been given the name of pellagra.

V.

TREATMENT OF PELLAGRA.

The pathogenesis of the intoxication with silica being known, it is easy to deduce the treatment; because a mineral acidosis could have no remedy other than an alkali. The greater difficulty is presented in the choice of an alkaline substance, which, used in intramuscular injection, circulates freely and does not damage the tissues.

We have chosen, therefore, trisodic citrate (sodium citrate), which is not caustic, circulates freely in the tissues, by burning out or oxidizing the organic part, leaves carbonate of sodium which neutralizes the free acid wherever present.

The first attempt at cure was made upon one of the dogs (No. 11, Tab. 5a, Fig. 16, 17, 18), which had served for the study of the urine under the action of colloidal silica, and which had been reduced to the conditions of captivity. And, to avoid the improvement from the effect of the suspension of the injections of colloidal silica alone, we continued these and at the same time injected daily 1 c.c. of a 5% solution of trisodic citrate. We saw the animal recover and the composition of the urine modified with equal rapidity and returned to the normal.

In the following table we report the analytic data which refers to this period of treatment and follows table No. 1a. Also in the graphics No. 16, 17, 18, are found traced the progress of the various determined substances also in this period and can be easily compared with those of a normal period in captivity and of periods of intoxication.

After 8 injections the animal was cured of the sickness caused by the silica and has reacquired all of its gaiety and vivacity and its former appetite.

TABLE 5a.

In One Liter of Urine.

Date, 1913.	Volume of urine, c. c.	Specific gravity.	Fixed substance. gm.	Ash. gm.	Cl. gm.	SO$_4$. gm.	PO$_4$. gm.	Alkali. Na. gm.
Feb. 23.	100	1.0396	88.00	17.07	3.261	4.123	10.903	4.545
26.	150	1.0247	42.40	14.30	5.388	2.823	6.112	4.427
28.	105	1.0272	44.00	13.33	4.750	2.456	4.625	9.050
Mar. 3.	110	1.0303	59.44	16.76	6.381	7.578	7.681	5.324
6.	130	1.0252	44.10	14.90	6.736	3.883	4.378	5.332
8.	150	1.0306	43.95	13.05	5.887	3.870	4.708	4.387
10.	125	1.0318	86.26	11.43	6.168	3.089	3.469	4.584
13.	184	1.0244	66.12	12.72	7.444	5.156	2.891	5.056
Mean	132	1.0292	56.28	14.45	5.752	4.122	5.596	5.338

In the Total Volume of Urine.

	Fixed Substance.	Ash. gm.	Cl. gm.	SO$_4$. gm.	PO$_4$. gm.	Alkali. Na. gm.	Sum of Ions in volume.	Difference between Ions and ash.
Feb. 23.	8.800	1.707	0.326	0.412	1.090	0.455	2.065	—0.358
26.	6.360	2.145	0.808	0.423	0.917	0.664	3.469	—1.324
28.	4.525	1.400	0.499	0.258	7.486	6.075	2.423	—1.023
Mar. 3.	6.538	1.844	0.702	0.834	0.845	0.586	3.573	—1.729
6.	5.733	1.937	0.876	0.505	0.569	0.693	3.051	—1.114
8.	6.593	1.957	0.883	0.581	0.706	0.658	3.334	—1.377
10.	10.783	1.429	0.771	0.386	0.434	0.573	2.462	—1.033
13.	12.166	2.350	1.370	0.948	0.531	0.939	4.161	—1.811
Mean	7.687	1.846	0.779	0.544	0.697	0.620	3.067	—1.096

Injected at the same time SiO$_2$ and a 5% solution of sodium citrate.

Encouraged by this result, we decided to apply the same treatment to pellagrins with the assurance of not doing them any injury with innocent injections of trisodic citrate and with the hope of doing them some good in case that pellagra were nothing else than a mineral acidosis, following the action of silica or of combinations of silica.

And behold the results of our experiment.

1. Natale Fioriti, daughter of Guiseppi, of 35 years, resident in the commune of Gualdo Tadino, division of Morano, region of Casa Gastalda.

Says she has been a pellagrin from birth; since then she has always had, in her memory, cutaneous manifestations and gastro-intestinal disturbances. Has always lived and worked in the country where she lives today.

Has never had any sickness worthy of special mention, except the disturbances stated above. Was always of slow intelligence and twice had recovered in the Pellagrosario Umbro in the City of Castello where she had restorative treatment besides good food, which was abandoned when she returned to the family.

Noted at once on a superficial examination the torpid state of the intelligence and the whole symptomatic picture of a pellagrin in an advanced state. The walk, the physiognomy, the characteristic eye, the tongue in ridges, the venous ectasis on the nose and on the zygomatic region, the exaggerated reflexes, the classical pellagrous gauntlet, etc.

She had been repeatedly and periodically visited from 1909 till today, not only by us, but by the members of the Ministerial Commission, by the Provincial Umbra and the English Commission for the study of pellagra, and was, in accordance with the sanitary officials of the place, Doctors Zaccheroni and Guerrieri, adjudged a classical pellagrin.

During last February (1913) she was placed under observation by us to determine the composition of the urine and its modification under changes of environment, of food or of treatment.

At first the urine was examined on the 4th, 6th and 8th days of February, leaving Fioriti in her home and with her habitual food, consisting of cakes of polenta (*light*) and a few vegetables seasoned with a little oil and onion.

In the second period which was from the 8th day to the 20th day of February, the patient was recovering in the hospital of Gualdo Tadino, where she received a healthy and sufficient diet and the urine was examined on the 12th, 14th, 16th, 18th and 20th days.

Then the patient was returned to her home and the urine examined on the 23rd day of February and the 2nd, 9th and 16th of March.

The results of these analyses are reported in the following table, referred to a liter of urine and not to the urine passed in 24 hours; since it was impossible for Fioriti to measure the volume when she was in her home and worked in the field. This defect we have supplied, in a manner, by putting in comparison the residue of the urine with the chlorin, on the supposition that diminishing the volume increased proportionally the amount of the residue and the amount of the chlorin and vice versa. We have chosen the chlorin and not any of the other determinate anions, because it is the one more prominent in pellagrins through the increased amount which is passed, and because it is an index of an exaggerated equilibrium between fixation and elimination.

TABLE 6a.

Natale Fioriti of Gualdo Tadino.

Date.	Sp. gr.	Resid. gm.	Ash. gm.	Ca. gm.	SO_4. gm.	PO_4. gm.	Cl. gm.	Na. gm.	Cl. Res. 100.
Feb. 4.	1.0235	51.25	21.45	13.54	2.028	1.074	0.207	6.698	26.43
6.	1.0212	41.47	18.85	11.49	1.297	0.991	0.124	6.099	27.70
8.	1.0208	39.80	20.03	10.92	1.224	1.165	.....	6.321	27.43
Mean	1.0218	44.17	20.11	11.98	1.516	1.076	0.165	6.372	27.18
12.	1.0248	56.32	17.12	11.138	2.555	2.478	0.0860	6.987	19.78
14.	1.0190	38.94	16.85	9.429	1.483	1.156	0.0162	3.762	24.21
16.	1.0252	55.08	18.19	9.217	2.425	2.891	0.0124	.....	16.73
18.	1.0234	45.92	21.07	10.422	2.071	2.313	0.1155	6.381	22.69
20.	1.0231	47.61	18.65	8.437	2.413	2.313	0.0126	4.210	17.72
Mean	1.0231	48.77	18.37	9.728	2.189	2.230	0.0485	5.335	20.22
23.	1.0237	46.91	18.95	8.863	2.016	3.634	0.0770	6.089	18.89
Mar. 2.	1.0216	40.29	19.57	9.642	1.667	2.560	0.0330	1.753	23.92
9.	1.0193	39.53	15.34	8.295	2.028	2.312	0.0640	4.445	20.98
16.	1.0237	46.03	20.43	10.506	2.296	2.147	0.0390	3.073	22.82
Mean	1.0220	43.19	18.57	9.326	2.001	2.663	0.0530	3.840	21.65
Apr. 2.	1.0267	57.50	17.44	7.019	1.516	6.106	0.0530	6.581	12.20
11.	1.0229	46.51	19.47	9.997	2.351	1.569	0.0569	5.147	21.49
16.	1.0210	43.83	17.88	8.649	2.075	1.734	0.0555	5.690	19.73
May 7.	1.0254	55.14	21.52	10.348	2.528	1.404	0.0630	7.984	19.67
19.	1.0247	51.05	20.05	10.138	2.357	1.899	0.1570	5.440	19.85
Mean	1.0241	50.80	19.27	9.350	2.165	2.542	0.0770	6.168	18.58

To Fioriti, *left in her own environment, at her own work and with her scant and uniform diet,* intramuscular injections were given of 1 c.c. of a 10% solution of trisodic citrate in the gluteal region, commencing on the 27th day of March and ending on the 28th of May except an interruption from the 16th of April to the 5th of May.

The urine was saved from time to time and the analyses of it are reported in the foregoing table.

At the same time the dynamometric variations and the weight were noted (1); took count of the improvement following and of the objective and subjective symptoms and calculated with approximation the percentage of hemoglobin (2).

Without entering into details, we recount briefly whatever of note we determined during the whole period of treatment.

Duration of treatment, 63 days.

Number of injections, 36.

Dynamometry:

Right hand increased from 25 kg. to 32 kg.

Left hand increased from 23 kg. to 30 kg.

Weight of the body, decreased from 69.300 kg. to 66.500 kg. (3)

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1. In calculating the dynamometric variations a Collin dynamometer was used. The test was repeated each week, giving attention to taking the strength three or four times at each test from both the right and left hands and recording the mean.

2. The percentage of hemoglobin is stated in only three of the patients. Given the difficulty encountered, since the examinations were made in a house in the country, where all the patients lived, it was not possible to follow the precise methods which in a special case are not used. We had recourse to the chromometric method, using the Hemoglobinometer of Boeringer, easily carried, and which, like that of Tallquist, is sufficient to give an idea sufficiently exact of the modifications which are taking place.

Hemoglobin increased from 50% to 70%.

Notable improvement of the disturbances of the stomach, which appeared especially during work; considerable increase of appetite; diminution and almost disappearance of the vertigo, increase of strength, greater endurance of labor.

Besides, as stating an indisputable fact, we noted that the erythema, which had been periodically manifest at the beginning of each spring, was not manifest this year.

Another sign of the continuing improvement of Fioriti with the treatment with trisodic citrate we found in the progress of the rapport $\frac{\text{Cl}}{\text{Residue}} \times 100$ which, in the mean, was 27.18, when Fioriti was in her home; decreased to 20.22 in the hospital under observation; rose to 21.65 on return to her habitation and occupation; fell to 18.58 under treatment. This signifies in reality that the excessive quantity of chlorin passed by Fioriti, a pellagrin in her own environment, was notably decreased by a change of diet, of environment and of potable water, but was still more notably decreased by the action of the treatment, when Fioriti was left *in her own environment and to her own alimentation*. Then, the urine tended to return to the normal and the trisodic citrate appears to have broken the exaggerated or pathological equilibrium of the mineral salts, formed by the action of the injurious substance, which to us is the silica or its compounds.

2. Carmela Celli, daughter of Serafino, of 19 years, unmarried, living in Gualdo Tadino, division of Grello, region of Case Castellari.

The disease commenced two years before with cutaneous

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[3] The diminution of weight, in this special case of Fioriti, is in rapport with the increase of labor to which she was subjected each day, having to walk, coming and returning, about 8 kilometers of bad road, to reach the place where the injections were given.

manifestations on the back of the hands and general lassitude. This was especially manifest with dizziness when the girl walked, and during the work in the field for which she cared. She had not been subjected to any therapeutic treatment. She had always lived in the division of Morano and only for a short time had moved into her present home. But she recovered in the place of treatment.

The appearance of the patient was discrete; the panniculus adiposus well preserved; the eyes tense, lucid, the tongue denuded of epithelium but smooth without fissures; the skin of the lower region of the forearm and the back of the hand was thin, lucid, with evident traces of former lesions. Had tremors of the hands, exaggerated reflexes, plain inequality of pupils.

Did not complain of digestive disturbances. Was depressed, cried readily, believed herself disliked and mistreated in the family and did not have any desire to go far from her own.

She was subjected to treatment the 27th of March and every day was given intramuscular injections of 1 c.c. of 10% trisodic citrate in the gluteal region, being left in her own home, at her own labor and with her own food. After a few injections, said she felt better; the dizziness which frequently attacked her became more rare and she felt more secure in walking.

On the 16th of April after 17 injections, said that *her legs no longer gave way and her head did not spin around as before.* On the 14th of May, she returned, after some days of absence, pleased to have her menstruation regular in time and quantity without disturbance of any kind as she had had before.

At this time the erythema was not present, the strength and weight were notably increased, confidence in herself returned with the consciousness of improvement.

The treatment of this pellagrin may be summarized thus:

Length of the treatment, 63 days.

Number of injections, 37.

Dynamometria:

Right increased from 18 to 21.

Left increased from 13 to 19.

Weight of the body increased from 52.700 to 54 kg.

Hemoglobin increased from 60% to 80%.

There was in effect: Disappearance of the lack of confidence in herself, disappearance of the vertigo. The walk became secure, the strength and the weight were notably increased; the menstruation appeared as it did at first. There were no further cutaneous manifestations.

3. Clementina Fischi, living in the commune of Gualdo Tadino, division of Grello, region of Fosse, 55 years, married.

About 25 years ago the first symptoms of the disease appeared, with a prevalence of disturbances of the digestive tract; almost at the same time erythema appeared and returned periodically each year without interruption. During all this period she was never in a pellagrous hospital, was treated twice in the hospital of Gualdo; the first time for 30 days, the second for 20 days. In this hospital as in her case, at various times they practiced constitutional treatment with iron, arsenic, cod liver oil, etc., but with little good result.

Always lived and worked in the country where she lives today and where she acquired the pellagra, although before marriage she lived elsewhere.

She has seven children and at 25 years was very sick, but there is no record of what disease.

At present is of total pellagrous habit; countenance dull, walk uncertain; eyes fixed, bleak; conjunctiva tense, lucid; lips white, tongue denuded of epithelium, with deep fissures which render it muriform; remains of erythema on the hands which present a skin intensely pigmented.

Suffered with pyrosis, bearing down pains of the stomach and abdomen, and had a sense of extreme weakness.

Has tremors of the hands, vertigo, loss of confidence in herself; cries about nothing, has exaggerated patellar reflexes.

Placed her under trisodic citrate treatment on March 27th, without change in her habits, without removing her from her home, without any modification of her diet. After seven injections stated she felt more *vivacious* and more *resolute* (sure of herself). At the 17th injection declared that she felt distinctly better, especially with regard to the stomach; felt stronger, ate with better appetite, and again entertained hope of recovery.

The treatment lasted 63 days.

Number of injections, 36.

Dynamometry:

Right from 15 to 20 kg.
Left from 13 to 19 kg.

The weight increased only 800 grams; from 45.100 to 45.900 kg.

Also in this pellagrin, besides the general improvement, the increase of strength and of weight, the erythema did not return this year, though, notwithstanding the constitutional treatment, it had returned periodically each spring for 25 years.

4. Filomena Martini, daughter of Serafino, deceased, living in the division of Morano, region of Monte Rampone, in the territory of the commune of Gualdo Tadino.

Is 38 years old and married. From the marriage seven children were born, of whom five are living. Did not have any severe sickness in infancy or adolescence. About 15 years ago suffered from a grave affection of the nervous system, the form of which is not now clear; it is only recorded that the doctor treating her desired to put her in an asylum. After some years, about ten years ago, commenced to manifest the cutaneous alterations of pellagra, which always appeared annually up to the spring of last year (1912). She did not yet have grave disturbances of the digestive apparatus; suffered only from time to time, with loss of appetite, nausea and weight in the epigastrium.

She had not been treated in a hospital or a pellagrous sanitarium and had had no medicinal treatment; always lived and worked on the farm where she made her home.

Now she has a discrete appearance, but has a *facies* distinctly pellagrous. Some venous ectasis on the nose and cheeks, lips white as if ulcerated, tongue in ridges, eyes tense, lucid. Tremors of the hands, reflexes exaggerated. Has no appetite and feels, after eating, a sense of weight in the stomach; suffers from vertigo, and experiences frequently a sense of faintness which causes her to stop when walking or to suspend her work.

Has an abundant leucorrhoea which has troubled her some years.

Was placed under treatment with trisodic citrate the 27th of March, 1912, by administering each day in the gluteal region an injection of 1 c.c. of a 10% solution.

From the first injections commenced to experience a sense of improvement, which progressed to a true improvement after nine injections. In fact she said that *she was not weak any longer*—(faint)—that she no longer felt the habitual distress in the stomach and asked that the treatment be continued until she *should be truly well.*

The appetite was also improved, the accustomed diet was no longer sufficient; the strength increased, and according to what she said herself, that before she was not *able to carry a bundle of firewood, now she could lift an ox.* The leucorrhoea diminished and disappeared after the 20th injection.

The treatment lasted 63 days.

Number of injections, 32.

Dynamometry:

Right from 20 kg. to 31 kg.
Left from 17 kg. to 29 kg.

The weight increased from 58.800 kg. to 60 kg.

The hemoglobin increased from 60% to 80%.

It was doubted that Martini would receive greater benefit from the treatment, since she had been sick for many years. In her, in fact, besides that there was no appearance of the erythema this year, there was a greater increase of strength and a notable increase of weight. Also the general conditions were improved, the obstinate leucorrhoea which afflicted her disappeared.

5. Clementina Natalini, living in Gualdo Tadino, division of Grello, region of Case Zanni, aged 69 years.

Says she has been sick more than 25 years. The first manifestations were: gastric disturbances resisting all treatment. Cutaneous erythema followed in the form of a gauntlet and the pellagrous mask. Notable psychic disturbances followed, for which she was treated three different times in the provincial asylum of Perugia. She was later kept for some time in the hospital of Gualdo Tadino where she was given constitutional treatment.

The rest of the time she has always lived in the above mentioned locality, where she is also found at present and where she has always worked in the field.

She has had six children and one abortion. Has not suffered from other disease worthy of note.

At the present, besides *all* the stigmata of pellagra, suffers from a chronic diffuse bronchial catarrh and an obstinate diarrhoea.

Was placed under treatment the 27th of March, 1913, and was given each day an injection of 1 c.c. of a 10% solution of trisodic citrate. She did not realize the distinct benefit of the treatment itself, since except a slight increase in strength and a notable improvement of the diarrhoea, which ceased entirely after the thirtieth injection, she did not say that she felt cured. The bronchial catarrh and a notable dyspnea continued to annoy her.

The injections were discontinued the 28th of May, after having accomplished the following:

Length of the treatment, 63 days.
Number of injections, 35.
Dynamometry:
    Right from 16 kg. to 17 kg.
    Left from 15 kg. to 16 kg.

The weight increased from 45.500 kg. to 46.200 kg.

The advanced age and the presence of a diffuse bronchial catarrh, were perhaps a hindrance in Natalini obtaining all the benefit that was desired; there remains the fact that the erythema appearing every spring for 25 successive years, did not appear at all this year.

6. Felicita Ragni, daughter of Vincenzo, deceased, living in the commune of Gualdo Tadino, division of Grello, region of Casa Castellari, about 60 years of age.

Says she has been sick for more than ten years; the sickness commenced with grave gastro-intestinal disturbances, to which were soon added cutaneous manifestations in the form of a gauntlet and the pellagrous mask. She was treated for these disturbances in the Pellagrosario of the City of Castello, where she was given constitutional treatment, which was continued irregularly in her case. There never was a true improvement. Always lived in the locality where she now lives. Has eight children and all were born at full term. Besides the disturbances noted above, had for some years a cystitis which was entirely cured.

Now presents the complete picture of the phenomena of pellagra and principally the suffering from the gastro intestinal disturbances consisting of a sense of painful weight in the stomach and of pyrosis. Has continuous vertigo and extreme weakness, the patellar reflex is exaggerated, is pallid, thin, with the mucosa of the lips white; the tongue streaked with irregular muriform cracks; the bulbar conjunctiva tense, lucid, expression of the face dull. Has a blepharitis. The intelligence is rather dull. Suffers from insomnia.

Commenced the injections on the 27th of March and continued to the 28th of May with an interruption of a few days from the 16th of April to the 5th of May.

After seven injections, declared she no longer felt a *burning* in the stomach and slept better. Later the improvement became progressive and at tht 18th injection, although there had been no modification of her habits of life or alimentation, she declared she no longer had *golluppi* (weight) in the stomach and that the pain and the *burning* had *divagato* (disappeared).

The results of the treatment may be summed up thus:

Length of the treatment, 63 days.

Number of injections, 34.

Dynamometry:
  Right from 14 kg. to 19 kg.
  Left from 14 kg. to 18 kg.

Weight increased from 47 kg. to 47.600 kg.

There was also in this pellagrin a very notable improvement in the general conditions and especially in the digestive; there was an increase of strength, a slight increase of weight, and the erythema, appearing periodically and intensely until last year, did not make its appearance this year.

7. Annunziata Tini, daughter of Giovanni, deceased, living in Gualdo Tadino, division of Grello, region of Broccaro, age 46 years.

Was a pellagrin for about ten years. Gastro-intestinal disturbances predominated, and every year had the classical vernal erythema only in the form of a gauntlet. There was here no place for treatment, and no attempt had been made to alleviate her suffering with medicines. She had always lived and worked as a country woman in the country where she now resides. She has borne 13 children, of whom 5 survive; has never aborted, has never suffered from sickness worthy of note.

The principal symptoms which she presented at the beginning of treatment were the following: Grave loss of appetite; marked sense of weakness, accompanied by a vague pain in the abdomen, especially in the epigastrium; also, muscular pains, which did not permit her to work and prevented her lifting even very light weights and wearied her at once if she tried to walk. The tongue was denuded of epithelium and covered with deep fissures; the lips were whitish and denuded of epithelium, especially at the corners; the eyes were tense, lucid;

the patellar reflex was exaggerated; there was tremor of the hands. The skin of the back of the hands and of the lower part of the forearms was pigmented, dark, furrowed with whitish streaks, thin, shining.

Commenced the injection of 1 c.c. of 10 per cent trisodic citrate on the 27th day of March and continued (except for a short interruption from the 16th of April to the 5th of May) to the 28th of May.

From the first injections, commenced to show improvement, as the gastric and muscular pains diminished and the appetite returned. After 10 injections, said she felt stronger and that her knees no longer gave way; in the morning she arose from bed refreshed and no longer experienced the sense of weariness which had tormented her before. Could lift without weariness of weight; had greater resistance to fatigue. Also her spirits were much improved, the hope of cure returned and with it a good humor and appetite.

The improvement ran a progressive course, and when the injections were suspended there was no disappointment, since, in a short time, we saw almost the total disappearance of the disturbances present uninterruptedly for so many years.

The duration of the treatment was 63 days.

The number of injections, 34.

Dynamometry:

Right from 14 kg. to 19 kg.

Left from 14 kg. to 18 kg.

The weight increased from 46 kg. to 47.200 kg.

There was in this patient a disappearance of the subjective symptoms and an increase in strength and weight. The erythema appearing constantly and periodically for ten consecutive years did not return in the summer of that year, nor the next.

8. Caterina Collarini, daughter of Bastiano, deceased, age 57 years, living in Gualdo Tadino, division of Morano, region of Monte Maggio.

It is not recorded with precision when the first symptoms of the disease appeared, but, without doubt, many years ago. They began as she says with cutaneous erythema in the form of the pellagrous gauntlet and at the same time digestive disturbances arose, and the strength notably diminished. For some years has had a uterine prolapsus.

Has lived always where she was born and is always occupied with work in the fields. At present, while having a physiognomy of sufficient intelligence, has a pellagrous appearance. The eyes are fixed and blear, the bulbar conjunctiva tense and clear, the lips white, the tongue muriform with numerous deep sulci. The skin is pale, pigmented, with some venous ectasis; that of the hands and of the lower dorsal portion of the forearms with all the characteristics of a progressive and repeated erythema.

Suffers in the stomach and abdomen with burning and with pain which becomes acute during the time of work; she felt so weak that it was difficult to do her work each day of the treatment of the case. She was not able to work in the field; felt a frequent vertigo accompanied by an intense headache.

Has tremors of the hands, exaggerated reflexes.

Was placed under treatment the 5th day of May and given daily injections of 1 c.c. of 10% trisodic citrate.

The benefit which she said she felt was a notable increase of strength and a cessation of the digestive disturbances. In fact, although the treatment lasted but a short time, since only 16 injections were made, it was possible to note an increase of dynamometry and a slight increase in weight.

Length of the treatment, 24 days.
Number of injections, 16.

Dynamometry:
Right from 20 kg. to 23 kg.
Left from 18 kg. to 21 kg.
Weight of the body from 53.200 kg. to 53.600 kg.

In the spring there was no recurrence of the pellagroderma.

9. Filomena Scaccia, daughter of Angelo, living in the commune of Gualdo Tadino, division of Morano, region of Monte Rampone, age about 47 years.

It appears that she had enjoyed good health until the age of 35 years, when she suffered from peritonitis. Following this grave malady, various disturbances of the stomach appeared and later cutaneous manifestations and psychic changes. She did not recover in the hospital nor in the pellagrosario, and with the exception of an absence of 5 years during which she lived in a non-pellagrous zone of the commune, lived always in the locality where born and where she became sick. Has taken some constitutional treatment which did not relieve her suffering, which rather grew continually worse.

Has four children, all still living.

At present has all the appearance of a pellagrin; expression dull; walk uncertain; mind obtuse; eyes fixed, blear, the bulbar conjunctiva is tense and clear; lips white; the tongue denuded of epithelium and furrowed with deep cracks which give it a muriform appearance; on the hands the remains of the pellagrous gauntlet. On the back of the hands and the lower part of the forearm the skin is shining brown, atrophic, thin and folded in hard wrinkles.

Suffers with burning and bearing down pains of the stomach and the abdomen.

Complains of intense pain in the head, a sense of being stunned, vertigo and insomnia. Has a complete loss of confidence in herself and is sure that she will never be well again.

The reflexes are exaggerated and the tremors of the hands are much accentuated.

Attracted by the good news which friends gave her, that she should receive treatment, she submitted herself to injections of trisodic citrate on the 7th day of May, which was given in a dose of 1 c.c. of a 10% solution until the 28th day.

Duration of the treatment, 22 days.

Number of injections, 16.

Dynamometry:

Right from 10 kg. to 16 kg.

Left from 10 kg. to 15 kg.

Weight of the body from 58.700 kg. to 59.350 kg.

In this patient; who presented a picture especially grave, the treatment was very short. On the whole there was a sensible increase of the dynamometria as in the weight and these were attended also by some improvement of the general conditions, as the erythema which had constantly appeared before, did not appear again.

10. Maria Cecini, daughter of Germano, deceased, married with three children, age 44 years, a porter (1).

Was of healthy physical constitution. Menstruated regularly and until the age of 26 years always enjoyed the best of health. Has a maternal uncle in an insane asylum; her parents were not related and were not disproportionate in age.

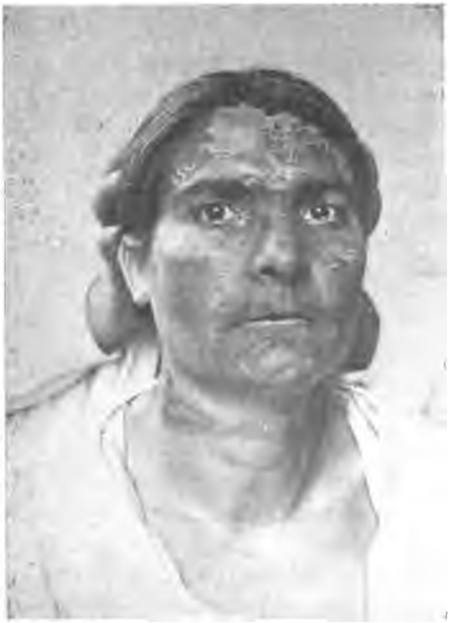

Fig. 25.

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(1) The record of this patient is taken from the records of the Provincial Insane Asylum.

A legitimate child not presenting anomalies of development. Did not abuse stimulants. She is nourished principally on bread and rice, has never made use of maize (granturco). Says she has eaten a little polenta scarcely once in 15 days.

Is of docile character, an indefatigable worker, has waited at a vineyard situated close to the locality of S. Cesareo (Commune of Zagarolo—Rome).

In 1896 suffered with a broncho pulmonitis and in the beginning of 1898, following a fright occurring in the first months of nursing, commenced to manifest nervous disturbances accompanied by headache and pains in the stomach. Her character was strongly altered, she beat the children, she sued her husband at law, talked always about religion, continually frequented the church, neglected the duties of the family. Was confined for these disturbances in April, 1898, in the insane

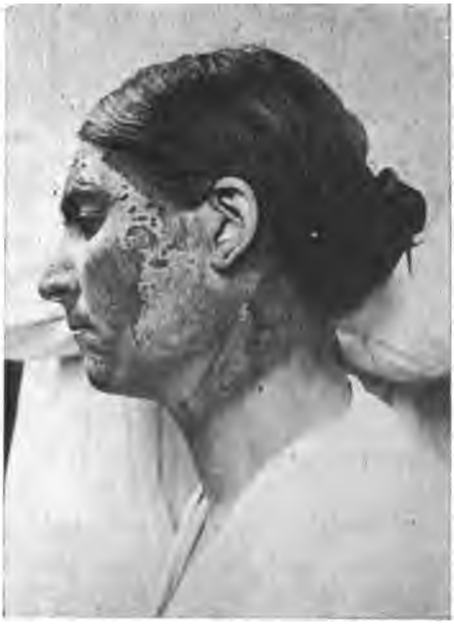


Fig. 26.

asylum in Rome, where she became subject to continuous hallucinations.

Subjected to treatment adapted to her condition she improved continually and progressively, so that in July, after three months residence in the insane asylum, she was discharged cured.

For a time did not have other nervous disturbances, but they appeared again accompanied by severe pain in the head and abdomen at the beginning of this year, 1913.

During the period of cephalalgia, she was so unstrung that she was constrained to remain in bed. Due to the alterations of her character she was interned again in the asylum, where she arrived in the observation department the 18th of April, 1913.

To the request that she recall the past she did not respond with exactness; did not recall what she had done or said; only remembered that she came up in a carriage and felt better from the air on the way.

Denied that she ever had convulsions; suffered instead from vertigo and a feeling of falling to the ground, losing consciousness for a short time. Dreams frequently of falling from a height and frequently wakens very much frightened. Always remains somewhat isolated, gesticualtes and talks with imaginary persons. Has a normal walk, normal sensibility and active and passive motility of the upper and lower limbs. Patellas normal. There is tremor of the extended hands and trembling of the eyelids. Intestinal disturbances do not exist; the tongue was bright red, denuded of epithelium especially on the borders; the lips white, cracked at the margins; the edges of the gums white; the eye tense, lucid. On the back of the hands, which was reddened, the skin presented superficial lesions with a thin crust and the remains of desquamation with a sense of intense burning. Weight, 56 kg.

On the 28th of April, after 10 days of residence in the hospital, noted an aggravation of the cutaneous lesions on the back of the hands. Observed an erythema and the vesicles ran together forming large scabs; at the same time symmetrical dark red spots appeared on the face and on the sides of the neck.

After some days (May 4) the cutaneous eruption spread, occupied the forehead, the nose, the zygomatic region, the chin and the sides of the neck (Fig. 25, 26).

On the back of the hands the vesicles broke and the skin denuded of corneal epithelium was dark red with abundant desquamation (Fig. 27). The patient being interrogated, remembered that the cutaneous erythema in the form of a gauntlet and mask appeared the first time about six years before and reappeared periodically each year at the beginning of summer. A diagnosis was made of *maniacal-depressive psychosis*, probably periodic in a pellagrous subject.

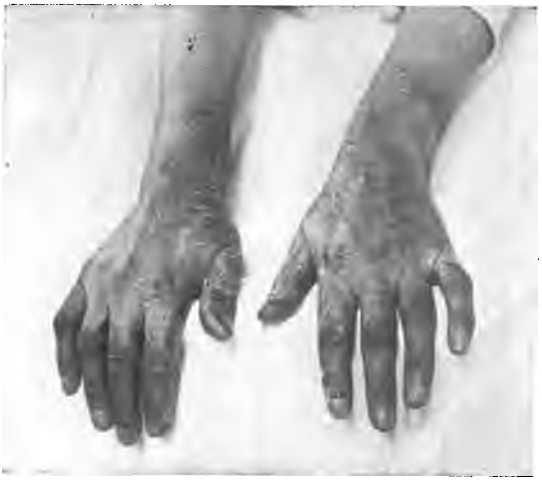


Fig. 27.

Called to visit the patient on the 16th of May, commenced the treatment with trisodic citrate with daily injections of 1 c.c. of a 10% solution.

After 8 days the erythema of the hands and face was much improved. There was no more exfoliation and the skin appeared uniformly red; it remained only on the sides of the neck. At the 15th injection noted no more traces of erythema on the back of the hands and on the face (Fig. 28, 29). The alterations on the sides of the neck already much improved, disappeared completely after the 24th injection.

While this local improvement was observed another, certainly not inferior, was recognized in the general conditions; the weight continued increasing and with it the strength. The urine scant, turbid on the first days, increased in amount and became limpid.

Only the nervous disturbances remained stationary. This was not surprising to us because the maniacal-depressive psychosis, a condition many years before the appearance of the first pellagrous symptoms, had nothing in common with the pellagrous psychosis. If, therefore, the treatment, as in the other cases was able to work such improvement in the manifestations of pellagra (erythema, adyamia, oliguria, etc.), no effect could be attributed to the other nervous disturbances.

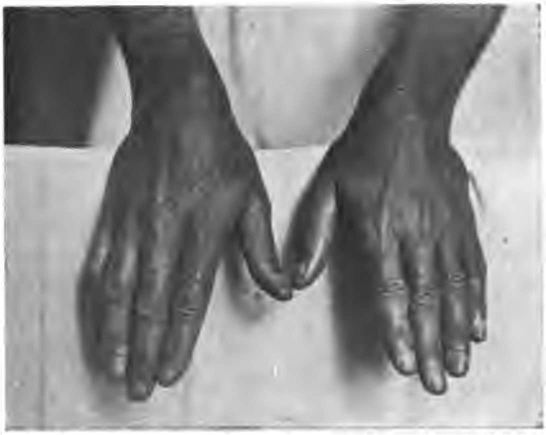


Fig. 28.

As to the benefit derived from the injection of trisodic citrate we have the tangible proof in the character of the curves of dynamometry, weight and quantity of urine which we have set out in Fig. 30.

Therefore, we conclude that also in this case, although the results may have been influenced by the residence of the patient in the asylum, in absolute repose and with the best food and by the concurrence of two diverse diseases, the treatment was most satisfactory, resulting in a very short time in disappearance of the erythema, increase of strenght and weight and the return of the urine of 24 hours to the normal amount, while in the period preceding the treatment during the residence in the hospital, it remained below the mean.

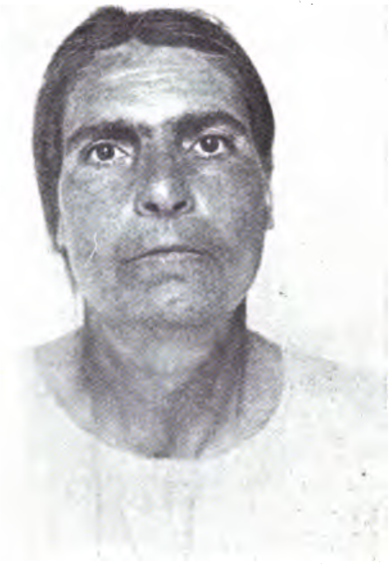


Fig. 29.

VI.

PROPHYLAXIS OF PELLAGRA.

The prophylaxis of pellagra, by us, is reduced to the provision of potable water, containing little silica and relatively much carbonate of calcium in solution; to the improvement of water containing much silica and little carbonate of calcium and the improvement of water opalescent or turbid with clay.

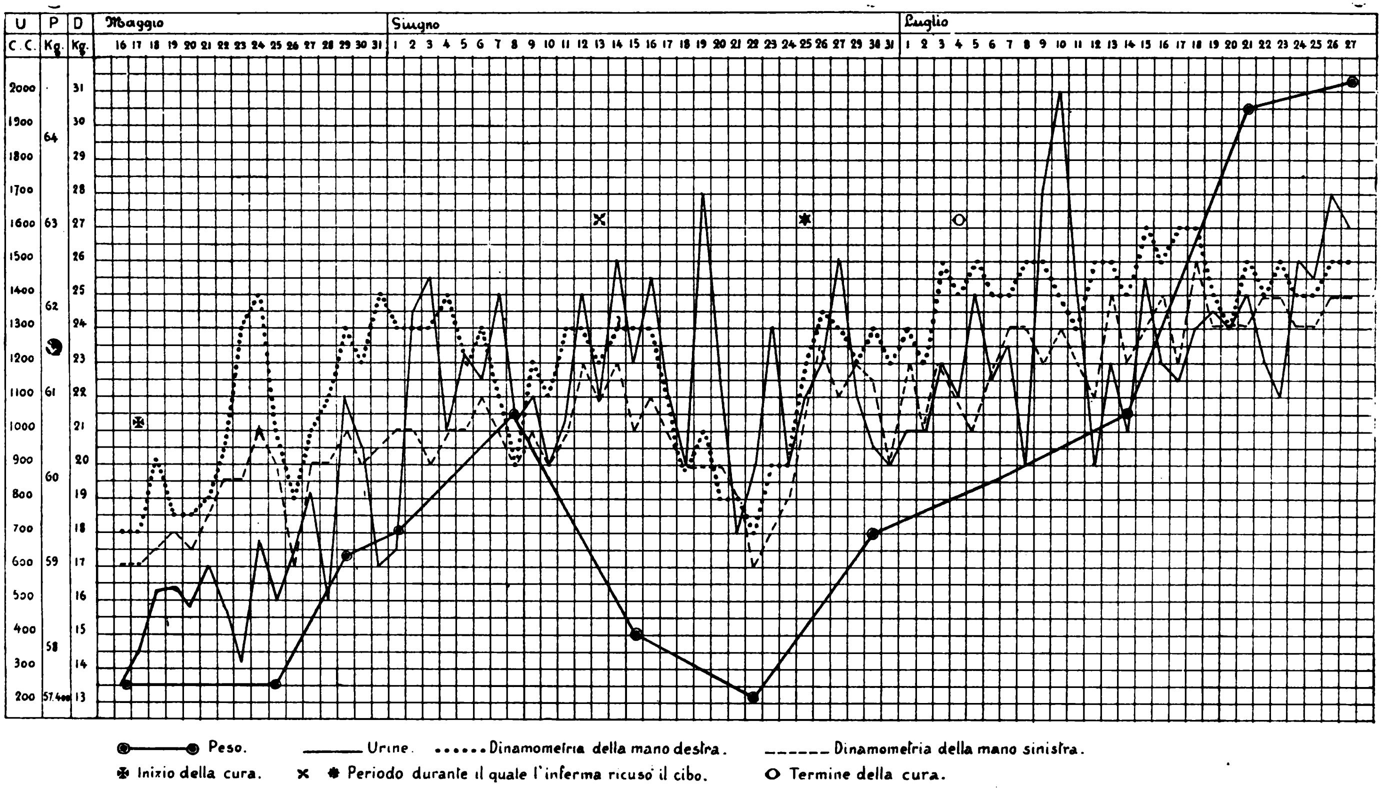
We do not believe that in a short time it is possible to provide all the potable water in the case of the inhabited country; but we do believe that it is possible to improve the rain water, and the water of small springs ordinarily collected in open ponds, having a very mobile clay bottom.

Therefore, we advise the collection of rain water, conveniently filtered in cisterns, and the water of small springs in wells, avoiding the entrance of rain water which erodes the surface and contains clay in suspension.

We advise, besides, to place in the bottom of the cisterns and of the wells a layer of small limestone pebbles of 20 c.m. at least in thickness, to prevent the stirring up of the clay bottom and to put into solution a sufficiency of carbonate of calcium in the rain water and in the water which does not contain any or contains but little.

In case that the collected water contains much silica and little carbonate of calcium, we advise also to place in the bottom of the reservoir broken limestone to a depth of 20 c.m. so that the carbonate may dissolve and neutralize the silica.

This prophylaxis being very simple and of little cost we hope that it will be accepted and put in practice by all in the pellagrous zones, because it is a measure of general hygiene


U
P
D
C. C.
Kg.
Kg.
Maggio
Giugno
Luglio
16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 30 31
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2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200
64 63 62 61 60 59 58 57.400
31 30 29 28 27 26 25 24 23 22 21 20 19 18 17 16 15 14 13
Peso.
Urine.
Dinamometria della mano destra.
Dinamometria della mano sinistra.
Inizio della cura.
Periodo durante il quale l'inferma ricusò il cibo.
Termine della cura.

Fig. 30.

which ought not to be omitted by anyone and especially by the sanitary authorities, for it is found no longer justifiable to follow the old customs or that they should not desire to distinguish the rural population from that of the cities and consider them inferior.

We believe that with this improved water pellagra can be made to disappear, as with a like improvement it has come to pass in many communes of the province of Padua, and especially in that of Este, where it is now limited to the one division of Ca'de'Borsetti, where nothing has been done to improve the water.

In fine, it is not inopportune to recall that in 1881, the Minister of Agriculture, with his circulars to the prefects of the Kingdom, suggested certain precautions to diminish pellagra among them, the provision of safe water in the country and the improvement of that which had not been made so.

And we believe it necessary that these same precautions regarding the water should be suggested today still more insistently, not only through a sentiment of social justice, but also to eliminate a pre-occupation which is certain to arise in the mind of each person who doubts the conclusions of our study, but does not doubt the facts established and related by us.

VII.

CONCLUSIONS AND CONSIDERATIONS.

From our experiments results the demonstration:

1. That silica, in colloidal solution and in the gelatinous state, produces a chronic intoxication in guinea pigs, rabbits, dogs and monkeys, when administered by hypodermic or intraperitoneal injection and by the mouth.

2. That upon this noxious action of the silica the electrolytes with which it comes in contact before it passes into the circulation, have a great effect, because they form colloidal compounds or superficial absorptions which are more noxious than the silica alone, or less, or no longer have a noxious effect, as happens with the carbonate of calcium.

3. That alumina has an action similar to that of silica, at least in the guinea pigs and the rabbits, and hence reinforces the action of the silica, whether it is united to it in the form of a colloidal combination, or is simply found in suspension in the water separate from the silica.

4. That the water of the pellagrous zone of the territory of Gualdo Tadino (divisions of Grello and Morano), containing clayey substance in suspension, administered by the mouth, mixed with bran, to guinea pigs, rabbits, and as a drink, to monkeys, has produced the same intoxication as the silica.

5. That the feeding of the animals subjected to the action of the silica with corn meal and herbs did not aggravate the intoxication, excluding by this that maize is able to contribute to the intoxication with silica, or with any other substance similarly noxious.

6. That the silica is the cause of a retention of salts which first results in an excessive fixation in the tissues and then in a liberation also excessive of mineral acids, which produce the disturbances and the anatomo-pathologic lesions already noted. For this reason, the silica in the intoxication acts indirectly instead of directly.

7. That the effects of this intoxication are neutralized by the intramuscular or subcutaneous injection of solutions of the neutral citrate of sodium as an alkalizer.

8. That the toxic picture produced by the silica in the animals is very similar, if not to say equal, to that of human pellagra.

9. That also human pellagra is an acidosis, as already demonstrated, and because the pellagrins are cured or greatly improved with injections of the neutral citrate of sodium: They are cured, that is, when the intoxication is relatively recent, or when the free mineral acid has not yet produced anatomical lesions no longer reversible, as on the other hand may occur in an intoxication of more ancient date.

10. That in the animals there were intoxications with a very short course, though not at all varying the common conditions of the experiment. And this agrees also with the cases of acute pellagra in man.

The facts by us ascertained and recounted in the foregoing conclusions demonstrate and confirm that natural potable and mineral waters are able to produce certain special states of the animal organism by altering its regular functions or by restoring them.

With the determinations made by us of the action of silica and of its relations with the electrolytes, undoubtedly a new chapter opens up in pathology and therapy and renders manifest the necessity of studying water more accurately and of taking account, not only of the absolute quantity of substance in solution but also of the proportion in which these same substances are found. Because from the analysis of today and from the knowledge of today it is not possible to draw any conclusion as to the safety of a water or as to its utility.

We are sure that many will not agree with these, our ideas, especially to those with regard to pellagra, either because they cannot be detached from deep-rooted convictions, or because of anticipations little favorable to us. And that this is so, we know from objections which have come to our ears from different parties who assert that silica and the water of pellagrous localities will not reproduce pellagra, but only a pellagrous syndrome.

But this syndrome is too similar to human pellagra, not so much in the cutaneous alterations, but especially in the clinical manifestations, in the microscopic and anatomo-pathologic findings and in the alterations of change, to be confounded with it. And only through an undesirable discernment they include our experiments with numerous others with good, sour and musty maize with which they produced it is true the death of the animals, though always with a partial syndrome, therefore very incomplete. And it should be noted that many of the experiments in which the herbivorous animals were fed with corn meal exclusively, withdrawing their water and the necessary cellulose of the herbs, were defective by the impropriety of the ration. And, therefore, many died and certain lesions of the skin and of the intestine were due exclusively to this same impropriety of alimentation and not to the real or imaginary toxins of maize.

We, instead, have fed our animals, not only by always maintaining their habits and taking count of their physiological needs, but by always furnishing in quantity the preferred food. Notwithstanding the lesions produced by the silica were always identical, always constant, by whatever way it was introduced.

And, therefore, we doubt that the thinning of the intestinal walls, produced for example in decumani, by Carbone and Cazzamalli (36), by giving them polenta to eat exclusively, has the same origin as that observed in pellagrins and in animals intoxicated with silica. Because it was probably due to abrasion of the mucosa by compression or by chemical action produced by the substances contained in the spores or in the moulds; while in the pellagrous and in our animals it was due to a true atrophy of the muscular coats, while the mucosa remained almost intact. *This indicates that in our case and in the pellagrous the cause of this atrophy is not mechanical, but chemical and endogenous, and as is interesting to note, more of a mineral than organic nature, because such properties are frequently met in the poisonous minerals (arsenic, thallium, etc.)*

Besides, the meaning of the syndrome is still modified in our favor, if the epidemiological investigation of pellagra is given due weight. They are in agreement in the assertion that this disease is not at all in strict relation, as is believed, with the consumption of maize (granturco) (37), but rather with potable water (38) and that it is strictly localized. And the older literature records some cases of pellagra without the intervention of maize, but the modern and the most modern records many more (39) and records also not a few cases of pellagra in children (40) from which it is certain maidism does not receive support, which it should not claim. Indeed it is overlooked entirely that it is not maidism and that it occurs without it. And if it is remembered that already about half the time has been spent in experimenting with spoiled corn and that from the experiments there is yet no clear proof, as was scientifically looked for, that the corn is the cause of pellagra, a spontaneous doubt arises in the mind of the impartial and from that doubt the question: if truly they are not found facing a real scientific *blunder.*

And to return to the objections which inexorably arise in showing the efficacy and the potency of the so-called poisons of maize or the poisons of special moulds, they have stated more hypotheses to arrive at an anaphylaxis *sui generis* (41), to which many have lent a hand less fortunately (42), and now it has passed from anaphylaxis to *monophagism,* destroying thus the toxic-zeism, so much caressed and defended, until now it has become simply *zeism* (43).

Neither does it detract from the proposition that we have searched in the literature to sustain that our syndrome is truly pellagra, because pellagra occurs in the brute animals which do not eat polenta, but are able to drink the water which intoxicates them. In fact, in the dictionary of agriculture of Marchese (44) we read as follows:

"It is manifest (pellagra) in diverse forms and with a variable course, has an evolution either acute or excessively mild, with phenomena less numerous or multiple, evident or entirely rudimentary. It is considered as an affection belonging to the human species, but now it rages among the bovine animals and also with less frequency among the other domestic species. In the bovine animals pellagra has an evolution mild and obscure; it changes, with time, to a progressive emaciation without obstructing greatly the different functions of the economy. In general, the authorities recognize in this disease three periods quite distinct: A failure of appetite, which is manifest at intervals; a certain disgust of liquid food, a diminution of the rotundity of the form, dirt eating, a perversion of taste, which prompts the animal to ingest substances extraneous to alimentation, disturbances of the respiration, dryness of the skin, which seems adherent to the tissues beneath, a strong disagreeable odor which develops from the whole surface of the body. Such are the principal manifestations of the first period.

The second period is characterized by the following symptoms: The skin is wrinkled and hairless in spots; the depravation of taste is more pronounced; the buccal mucosa is dry, wrinkled, inflamed; the leanness always becomes worse; the expression shows hebetude; the eyes are sunken in the orbit; the look is without expression. Soon the locomotion becomes difficult; intermittent febrile attacks, chills and tremors are manifest.

In the third period especially the nervous phenomena occur. The febrile attacks are frequent and the animals rush against resisting bodies (manger, columns, walls) which are excitants to them; they paw the ground; they open the mouth;

they try to bite and make a sound of plaintive bellowing. They finally die in one of these attacks.

During this last period an abundant diarrhoea appears, entirely liquid and extremely fetid."

Unfortunately an accurate and systematic research has not been made upon the animals of pellagrous localities, but nevertheless we have an abundant material now which leaves no doubt of the existence of pellagra among them as we know it in man.

In fact, one of us (Alessandrini) who has conducted an inquiry in the proposition in the commune of Gualdo Tadino, has established that in this territory there is known, especially among the cattle, a disease commonly called *tignuola,* which is manifest in the spring with a depilation in spots on the sides of the neck, the breast, and in cases more grave, also on the back; with decrease of strength and general decline. All these phenomena disappear with the coming of winter, but are manifest again in the coming spring.

Only those animals are subject to this disease which live in the country where it extends to the dogs and also to the cats living with pellagrous families.

To all of this, which our opponents ought to consider seriously, is added the treatment which was scientifically deduced from the animals intoxicated with silica and which succeeded with much satisfaction in not a few pellagrins. This treatment has been called by others a happy crowning of a study conducted with rigorous scientific method; but to us it seems an insufficient title. Because it suggests that the favorable results were due more to the influence of other factors than to the medicament. Nevertheless, we have already said in our preliminary note that "the treatment practically excluded any cause of error, in such a manner that any benefit which should be derived was not possible to be attributed to any other reason. The pellagrins were not moved from their habitations, there was no change in the food, nor diminution of labor" (45). And to document all not satisfied with our word, we report a letter directed to one of us from a sanitary official of Gualdo Tadino, Dr. Ruggero Guerrieri, who, with so much abnegation, conscientiousness and fairness, has followed and checked our experiments, and with this we conclude our memorial.

Gualdo Tadino, August 20, 1913.

Most Esteemed Signor Professor:

I have finished the second period of hypodermic treatment administered to a group of pellagrins, chosen in the territory of Grello and Morano, exhausting all the phials so nobly sent by you, and have in consequence advised the patients that the injections will be suspended for a time at least.

The pellagrous subjects feel so much improved that they have met the notice of suspension of treatment with displeasure, because they fear they will return to their former condition.

The fact is truly impressive that those, in this year, for the first time since they were attacked by pellagra, not only have not had any cutaneous manifestations, but showed more vigor and a greater comfort.

So much more is the fact notable, by recalling that the subjects which were subjected to treatment, were selected by me from the more grave, among those which, as you well remember, I showed them when you came with Professors Gosio, Giannelli and Antonini of the Ministerial Pellagrological Commission and which were also observed by Prof. Pisenti of Perugia, and by the English Commission of Sambon and Chalmers.

I am able to assure you that these same pellagrins have always lived, during and after the treatment, in the conditions of environment to which they were accustomed, poorly nourished as in the past. To what, therefore, can such improvement be attributed, if not to the therapeutic treatment to which they were subjected?

Tell me if I should make another experiment in the matter, and in an affirmative case, it would be well to send me a notable quantity of phials. The evident improvement of the subjects has made an impression in the pellagrous zone of this

Commune, and if we should give attention to all those who desire to be subjected to the injections, it will be necessary to create a proper service.

At present, in expectation of your directions, I distinctly salute you.

Most devotedly,
DR. RUGGERO GUERRIERI.

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PART TWO

CHAPTER I.

PELLAGRA IN THE UNITED STATES.

The last few years have seen much interest manifested in the study of pellagra. For a long time it was thought to be a foreign disease. Mistaken theories as to its cause led physicians to believe that it would not invade America. Doubtless many cases were not properly diagnosed and the mild or incipient cases were overlooked entirely. Because of the peculiar and obscure manifestations of pellagra, it has been diagnosed and treated as "stomach trouble," "nervousness," "insanity" and as variously named skin diseases. Recently it has been discovered that there are thousands of people afflicted with pellagra in the United States. From causes which will appear later, by far the greater number of these cases are found in the Southern States. This is not because of any unsanitary condition or a pollution of the soil or water supply. The accusation that the people of the south are underfed or improperly nourished is a rank injustice. Pellagra is not caused or propagated by any fly, mosquito or gnat indigenous to the southern states. It is no fault of the people of the south, nor of their mode of life or sanitary environment that they are the victims of pellagra. It is not even due to their subtropical climate. Pellagra is due to a natural condition of the soil of the southern states over which the people have no control.

A better understanding of the distribution of pellagra in the world may be gained from the following brief:

History.

Pellagra is also known by a number of other names. The name pellagra is from the Italian, *pelle,* skin, and *agra,* rough. It is the name applied to the disease by the common people of Italy. It was introduced into medical literature by Frapolli who spelled it "pelagra." This same spelling may still be found in some Spanish writings.

The date of the first discovery of pellagra is unknown. It is naturally a disease of a settled agricultural people in a well worn agricultural country. Its description in medical literature is therefore necessarily modern. It is generally conceded that the first medical description was given by Gasper Casal, who had recognized the disease among the people of northern Spain. It was called "mal de la rosa" because of the peculiar redness of the skin in the cutaneous manifestations. Casal thought it was "a peculiar kind of diseases consisting of a combination of scurvy and leprosy." The same disease was called "Alpine scurvy" by Antonio Pujati twenty years later. Pujati studied the disease in the district of Feltre in northern Italy. Casal had made his report from Asturias in 1735. It was not until 1771 that Frapolli of Milan published his account and gave the name "pelagra," which is still retained with the new spelling of "pellagra."

From this time on for many years there was much written about this disease. The principal interest seems to have centered in Italy. In fact Italy was the one country in Europe destined by fixed character of population, age of agriculture and geology, to be afflicted with pellagra. So the publications of Zanetti, Odoardi and Gherardini followed. A large part of Italy was then under Austrian rule, and a hospital or "pellagrosario" was established at Legnano, by Joseph II of Austria. Gaetano Strambio, who had charge of this hospital for pellagrins, studied the disease there and published many works. The various writings of the period led to the establishment of the identity of pellagra, Alpine scurvy and mal de la rosa.

Once recognized, the disease was soon known to be quite prevalent in Italy. At this time it was quite severe and the mortality was high. It was studied a great deal and much was written.

The disease has been recognized in France, Roumania and Egypt, and reported from the other countries bordering on the Mediterranean Sea. The French medical literature on pellagra is not nearly so voluminous as the Italian. There is comparatively little in the Spanish. Until of late not much has been written in English. The Italian literature is very voluminous and until the last three years perhaps Lombroso was the leading authority. One of the first French writers was Hameau who called pellagra "maladie de la Teste," from the fact that he discovered the disease in the vicinity of Teste-de-Buch. Roussel of France has made valuable contributions to the literature of pellagra. Theodori has written of the disease in Roumania. Pruner reported the disease in Egypt in 1847.

Since the United States was comparatively a new country, it is natural, from the very nature of the disease, that it should be unknown here for many years. At the most the agricultural history of the Atlantic Coast is measured by two hundred years, while that of the Mississippi Valley is comprised in fifty years. There was a great deal of new land. The agricultural population was not fixed. People could move readily from one place to another. Persons who had lived in one place long enough to contract some of the symptoms of pellagra might move only a short distance, and in the course of a few months or a year all the symptoms would disappear. The soil was new. It still contained its virgin alkalies. The surface was rich in the humus of the ages. Deforestation with its attendant erosion was unknown. The hills and the valleys were not denuded and the gullying of farms had not taken place. The essentials in the epidemiology of pellagra were wanting, and it was not reported in America until about 1864, when cases were reported from New York and Massachusetts. It is worthy of note that the first reports came from the regions where pellagra would be expected.

Then there is a break of about twenty years in the American history of pellagra until it was reported in New Orleans, in North Carolina, Atlanta, and at Mount Vernon, Alabama. In 1907 it was found in the State Insane Asylum at Columbia, South Carolina. In another year it was recognized that pellagra prevailed over the southern states. It has not been so prevalent in the northern states for reasons which will appear. However, this is not due to climate or sanitary conditions.

In this connection a paragraph from Roussel of France who wrote in 1866, and who was instrumental in identifying pellagra and mal de la rosa, is very suggestive:

"Recently this malady has invaded new countries, and today it is found to the south of 47° of north latitude, between 10° of longitude west and even beyond 25° of longitude east, meridian of Paris, extending over a long zone of the temperate region of Europe from Cape Finisterre to the banks of the Sereth, across the Pyrenees Provinces of Spain and of France, upper and central Italy, and in the basin of the Danube, upon the eastern and southern slopes of the Carpathians even to the frontiers of the Russian Empire."

In the light of modern investigation, the foregoing statements of Roussel are very interesting. With the fixing and increase in density of the farming population, the increase of the farmed area, the destruction of forests, and the wearing out of the soil, pellagra has continued to invade new areas. From this it will be seen that there are but few areas in the world into which pellagra may not go. It is now reported from some districts almost all over the world and is most prevalent in Italy, Roumania, Austria-Hungary and the Southern United States. Italy and Roumania are said to have had as many as 100,000 cases each at one time with a very high mortality. The writer recently received a letter from Prof. Alessandrini of the Institute of Experimental Hygiene of the University of Rome, under date of May 14, 1915, in which he makes the following statement as to the distribution of pellagra in Europe.

"Per l'Europa si va che la malattia e' distribuita al Portogallo settentrionale, ad alcune regioni dello Spagna e dell'Italia, al sud della Francia, nel Tirolo Austriaco, nell'Ungheria, in

Croazia, Dalmazia, Bosnia, Serbia, Bulgaria, Grecia, Rumenia e Bessarabia. L'endemia pellagrosa pero e' maggiormente localizzata nell'Italia, nel Tirolo ed in Bessarabia."

"Through Europe the disease is distributed from northern Portugal to certain regions of Spain and Italy, to the south of France, in the Austrian Tyrol, in Hungary, in Croatia, Dalmatia, Bosnia, Serbia, Bulgaria, Greece, Roumania and Bessarabia. Endemic pellagra is especially localized in Italy, in the Tyrol and in Bessarabia."

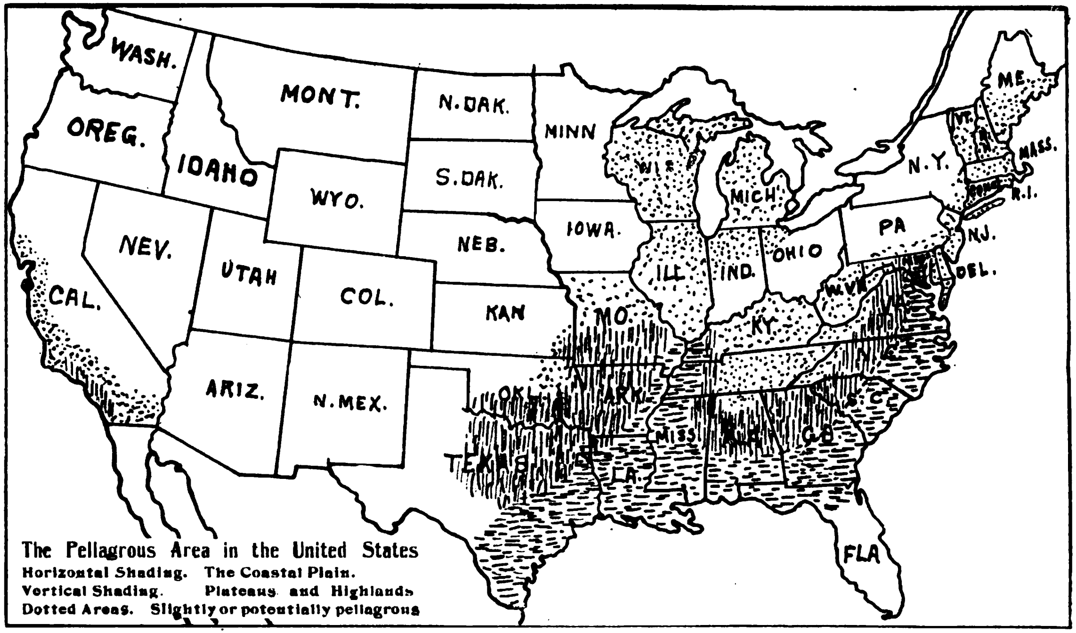
The United States Public Service has estimated that there were 30,000 cases in the United States up to and including 1911.

CHAPTER II.

GEOGRAPHICAL DISTRIBUTION IN THE UNITED STATES.

In a disease of this nature it is but natural that there should be an analogy between its distribution in foreign countries and in America. From the distribution indicated in Europe in the foregoing paragraphs, attention is called to the common school geography. It will be noted that pellagra is found upon the short slopes and narrow plains extending from the Pyrenees, the Alps, the Appennines and the Carpathians to the Mediterranean and Black Seas. The great inland plains are as yet comparately free. Lower Egypt, for ages the seat of a teeming agricultural population and annually washed by a flooded Nile is a pellagrous country.

So in the United States pellagra would naturally be expected east of the Appalachian Mountains from Maine to Florida, northwest of them to the Ohio and Mississippi rivers, south of the Ozark, Boston, Oachita, Arbuckle and Wichita Mountains to the Gulf of Mexico. From the very nature of pellagra it would be expected to prevail to a much less extent over Wisconsin, Michigan, Illinois and Indiana to the southern limits of the glacial drift. Up to the present it would naturally be expected to be very rare in Minnesota, North and South Dakota, Iowa, Nebraska, Kansas, Colorado, Wyoming, Montana, Idaho, Utah, Nevada, Arizona and New Mexico. It should be much more prevalent in southern Oklahoma than in northern Oklahoma. To a limited degree pellagra should in time be found on the Pacific slope.



The Pellagrous Area in the United States
Horizontal Shading. The Coastal Plain.
Vertical Shading. Plateaus and Highlands
Dotted Areas. Slightly or potentially pellagrous

Pellagra is very prevalent in Virginia, North and South Carolina, Georgia, Alabama and Mississippi. Only a comparatively small part of Virginia and the Carolians is really mountains, and this is confined to the western ends of these states. By far the greater part, the eastern part of these states is comprised in the coastal plain and plateau reaching west to the mountains. The same is true with respect to the northern and southern parts of Georgia, Alabama and Mississippi. Florida, Louisiana and Texas are also within this coastal plain.

There was little attention paid to pellagra in the United States before 1910. The statistics of deaths from that time on are only complete for the "registration area." In some other states there are statistics from the larger cities. In 1910, 368 deaths from pellagra were reported; in 1911, 659; in 1912, 674; and in 1913, 1,015, distributed to the registration area as follows:

California	19	Missouri	23
Colorado	3	New Hampshire	2
Connecticut	4	District of Columbia	10
Indiana	4	New Jersey	8
Kentucky	104	New York	7
Maine	10	N. Carolina Cities	157
Maryland	14	Pennsylvania	7
Massachusetts	13	Rhode Island	9
Michigan	8	Vermont	3
Minnesota	2	Virginia	165
Washington	2	Wisconsin	5

Large cities in states without the registration area report deaths from pellagra in 1913 as follows:

Alabama	91	Louisiana	53
Florida	19	South Carolina	56
Georgia	138	Tennessee	57
Illinois	5	Texas	17
Kansas	6		

Lavinder in Reprint from Public Health Reports No. 106, estimates that from 1907 to 1911 inclusive there were 25,545 cases of pellagra in the United States. In this estimate the states reported are as follows:

Eight states	15,870
Estimated	4,000
Maryland	25
Tennessee	2,500
Florida	250
Arkansas	500
Texas	1,500
Illinois and Pennsylvania	700
All other states	200

In Reprint No. 137 he makes the estimate for the same period for Arkansas, Oklahoma and Texas as follows:

Arkansas	945
Oklahoma	472
Texas	2,628

The Pellagra Commission of Tennessee in 1911 estimated that there were 2,500 cases of pellagra in the state. From September 1, 1912, to August 31, Texas reports 656 deaths from pellagra. The latest data from Texas reports 79 deaths in May and 94 in June, 1915.

California.

The deaths from pellagra in California in 1912, 1913, 1914, and from January to August, 1915, were as follows:

1912	9 deaths.
1913	18 deaths.
1914	27 deaths.
Jan. to Aug. 1915	19 deaths.

The geographical distribution of deaths for these four years is illustrated in the accompanying spot map.

Tennessee.

Repeated request elicits no information as to the prevalence and distribution of pellagra in Tennessee. Prof. James W. Jobling, of Vanderbilt University Medical School, states that his department has collected a list of about seven hundred cases.

Kentucky.

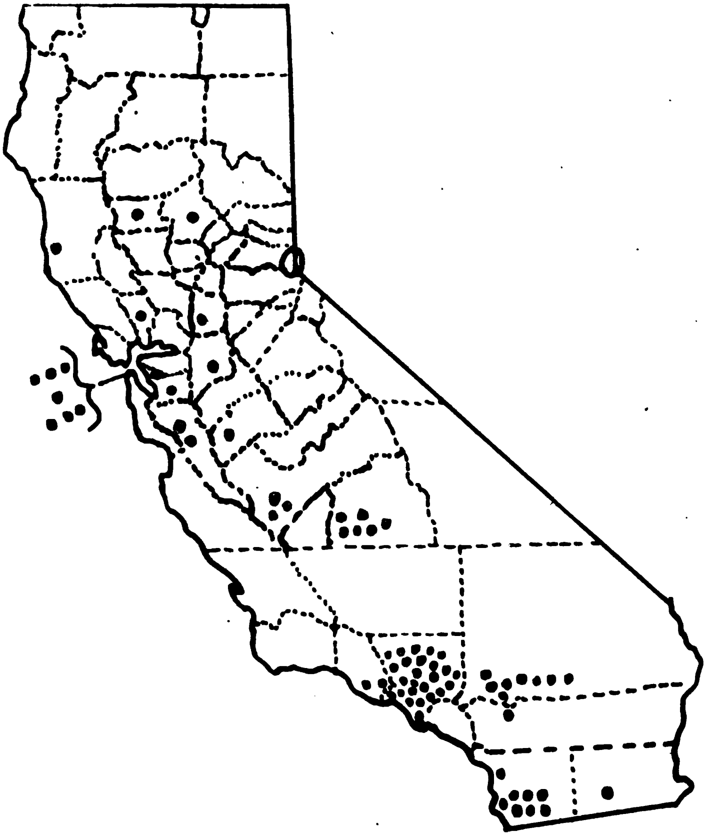
Repeated inquiry from the Secretary of the State Board of Health finally brought the statement that ninety per cent of the pellagra in Kentucky is found in the southeastern part of the state.

Arkansas.

No further information was secured from Arkansas.

Connecticut.

Connecticut reports four deaths from pellagra in 1913, and three in 1914.



Pellagra in California 1912—1914.

Kansas.

In Kansas there were 29 cases of pellagra reported up to the 7th of October, 1915. Fifteen of these cases were reported from Galena. The others were scattered throughout southeast Kansas.

Dr. S. J. Crumbine writes that it is altogether likely that with the unreported cases there are in the neighborhood of 35 or 40 cases in the state in the current year. Some of the reported cases have died in the meantime.

When the geology of Kansas is considered, it is of great importance to note that the city of Galena from which the greater number of cases was reported, is in the extreme southeastern corner of the state in the southeastern corner of Cherokee county. It is in the lead and zinc mining district on the western flank of the Ozark highland. The soil of Cherokee county, and of a large part of southeastern Kansas, is derived from the Cherokee shales, which were deposited from the early erosion of the Ozark highland. These shales have a large area, and average about 500 feet thick. Because of submergence and elevation, their surface soils were originally sufficiently alkaline to be prairie. Because of the base and origin being essentially highly silica, the alkalies have been leached out, and pellagra is appearing. With the continued erosion and leaching of these soils, pellagra can be expected to extend its area in southeastern Kansas. The frequency of cases within the area already affected may be expected to increase. The scarcity of alkalies in these soils is shown in the partial analysis of the Oswego Silt Loam, Kansas.

Maryland.

Under date of October 16, 1915, Dr. C. W. G. Rohrer, of the Bureau of Communicable Diseases of the state of Maryland, makes the following detailed report.

1905	1 case.
1909	3 cases.
1910	9 cases.
1911	12 cases.
1912	6 cases.
1913	11 cases.
1914	7 cases.
1915	17 cases.

In the necessarily extensive correspondence entailed in securing data from all the pellagrous states, nothing has given greater satisfaction or been more illuminating than the statements of Dr. Rohrer. In a paper which he presented to the second triennial meeting of the National Association for the Study of Pellagra, Columbia, S. C., October 3-4, 1912, he says nothing about corn, simulium flies, or deficient proteid diet, but does make the following remarkable statement:

"Down to the present writing (September 25, 1912), there have been 31 cases of pellagra accredited to the State of Maryland. Nine of these individuals developed the disease in the city of Baltimore, while 22 were county cases. *All have occurred in the Coastal Plain and in the Piedmont Plateau,* where the rainfall is greatest and the *soil composed of sands, clays, loams and marls.* Not a single instance of the disease has been found in the higher, drier, more elevated portion of the state, known as the Appalachian Region."

The Italics are ours. The epidemiologists studying pellagra in the United States have ignored these observations of Dr. Rohrer for over three years.

Missouri.

There were 14 deaths reported from pellagra in Missouri in 1913, and 24 in 1914. These are indicated in the outline map of Missouri, the deaths for 1913 being indicated by open circles and those for 1914 by closed circles.

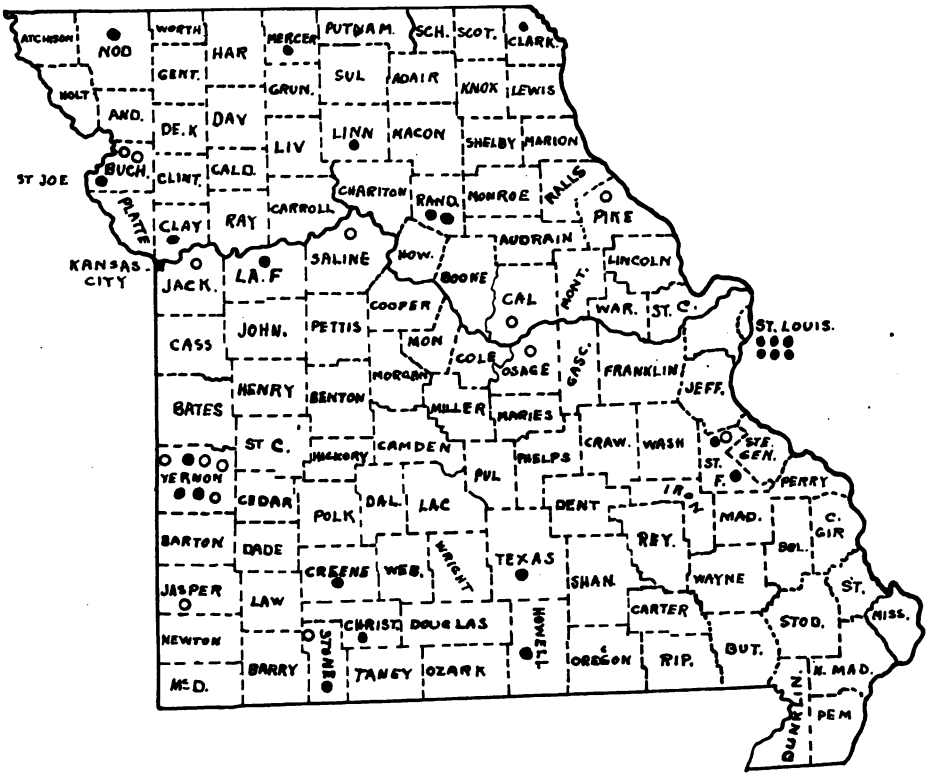
These cases are recorded for the two great physiographic divisions of Missouri, the Ozark Highland, which occupies almost all of the state south of the Missouri river, and the Glaciated Area which occupies all of the state north of the Missouri river.

Michigan.

Michigan has had two deaths and two other reported cases in the past five years. Two were from the Upper Peninsula and two from the Lower.

New York.

No cases of pellagra are known to the New York State Department of Health at the present time. Two deaths have occurred in the last two years, both in hospitals for the in-



Pellagra in Missouri 1913—14.

sane, one at Ogdensburg, the other at Central Islip, Long Island.

New Hampshire.

There have been approximately fifteen deaths from pellagra in New Hampshire in the last five or six years. About half of these occurred in the New Hampshire State Hospital, an institution for the care of the insane. Two or three others occurred at county institutions. The others were scattered throughout the state.

Mississippi.

For the year 1914 there were 10,954 cases of pellagra reported to the State Board of Health through the county health officers, as compared with 6,991 for the preceding year. This shows more of an increase than probably actually existed, but without fear of contradiction, it can be said that pellagra is increasing at an alarming rate. The basis for this assertion is based on the increase for the year 1914 in the number of deaths from this cause, as compared with that for the year 1913. With practically the same number of deaths from all causes reported for the two years, the number of deaths reported from pellagra for the year 1914 was 1,192, as compared with 795 for the year 1913.

The death rate for 1914 was 62.7 per hundred thousand population, as compared with a rate of 42.4 for 1913. This means that the death rate for 1914 increased over 47 per cent over that for the year 1913.

Pellagra is one, if not the most important, disease with which we are confronted at this time, and it deserves more attention than it has received to date. During the year 1914, in the number of deaths it was third, being only exceeded by tuberculosis and pneumonia. Pellagra caused more deaths during this year than typhoid fever, small-pox, measles, scarlet fever, influenza, epidemic cerebro-spinal meningitis and acute poliomyelitis combined. Pellagra affects both whites and negroes; for the year 1914 the white rate was 30.8, and the negro rate nearly three times as large, being 87.6 per hundred thousand population.

The mortality from pellagra, based on the number of cases reported for all deaths, was 10.9 per cent; white mortality 6.4 per cent and negro 13.4 per cent. On this basis the negro mortality is more than twice that of the white.

Pellagra is not confined to any particular section of the state, as it was reported from every county in the state, and every county had deaths from pellagra for the year 1914, with the exception of Hancock, Pearl River and Winston. The greatest number of deaths from this cause was reported from counties having hospitals. Hinds lead with 170 deaths; Lauderdale, 71; Adams, 53. The other counties having more than 30 deaths were as follows: Sunflower, 52; Coahoma, 46; Warren, 43; Bolivar, 40; Lowndes and Panola, 37 each; Forrest and Washington, 32 each, and Copiah 30.

Mississippi Health Bulletin, August, 1915.

Vermont.

Under date of October 11, 1915, Dr. Charles F. Dalton, Secretary of the State Board of Health of Vermont, reports deaths from pellagra in Vermont as follows:

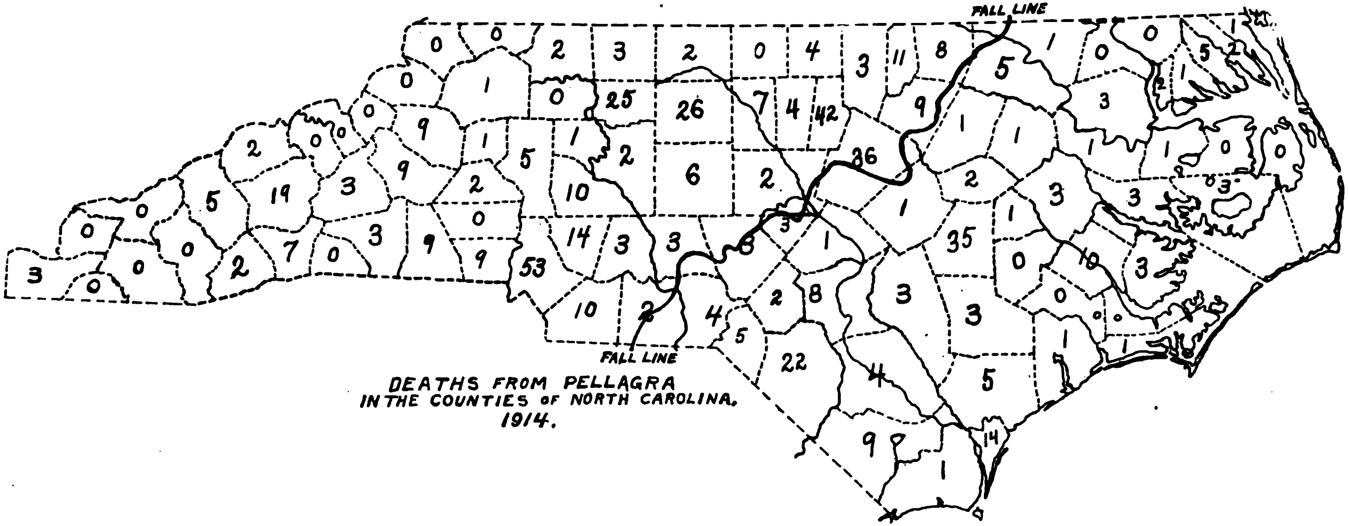
1910	2 deaths.
1912	3 deaths.
1913	2 deaths.
1914	2 deaths.

Massachusetts.

The Commissioner of Health of Massachusetts reports 28 cases and 7 deaths from pellagra in Massachusetts in 1915 up to October 9th. These cases are widely distributed in various parts of the state.

North Carloina.

North Carolina, because of lying almost entirely within the Coastal Plain and Piedmont Plateau regions, is one of the distinctly pellagrous states. The North Carolina Bureau of Vital Statistics reports 551 deaths from pellagra in the counties in 1914, and 231 cases of death in the cities of one thousand inhabitants or more. The geographical distribution of pellagra in North Carolina is indicated on the accompanying outline map.



DEATHS FROM PELLAGRA
IN THE COUNTIES OF NORTH CAROLINA.
1914.

Florida.

Dr. Joseph Y. Porter, State Health Officer of Florida, under date of October 11, 1915, reports that from the results of a survey now being made, pellagra is more prevalent than it was believed to be. The greatest prevalence is in the western part of the state. Recently seventy cases were found in three small communities in one county west of the Chattahoochee river.

Alabama.

Pellagra is very prevalent at this time in the state of Alabama. It is a matter of increasing concern to the health authorities. The deaths in 1913 were 500 and in the first ten months of 1914, 711. The prevalence and distribution of pellagra in Alabama are illustrated in the accompanying outline maps.

Louisiana.

Under date of October 25, 1915, Dr. Oscar Dowling, president of the State Board of Health of Louisiana, reports: "From May 1 to October 1, 1915, there were officially reported 960 cases showing patients in 59 parishes varying from 1 to 247. The largest numbers are as follows: Caddo, 247; De Soto, 207; Morehouse, 136; Vernon, 90; Sabine, 72; Bossier, 23; Rapides, 22; Bienville, 14."

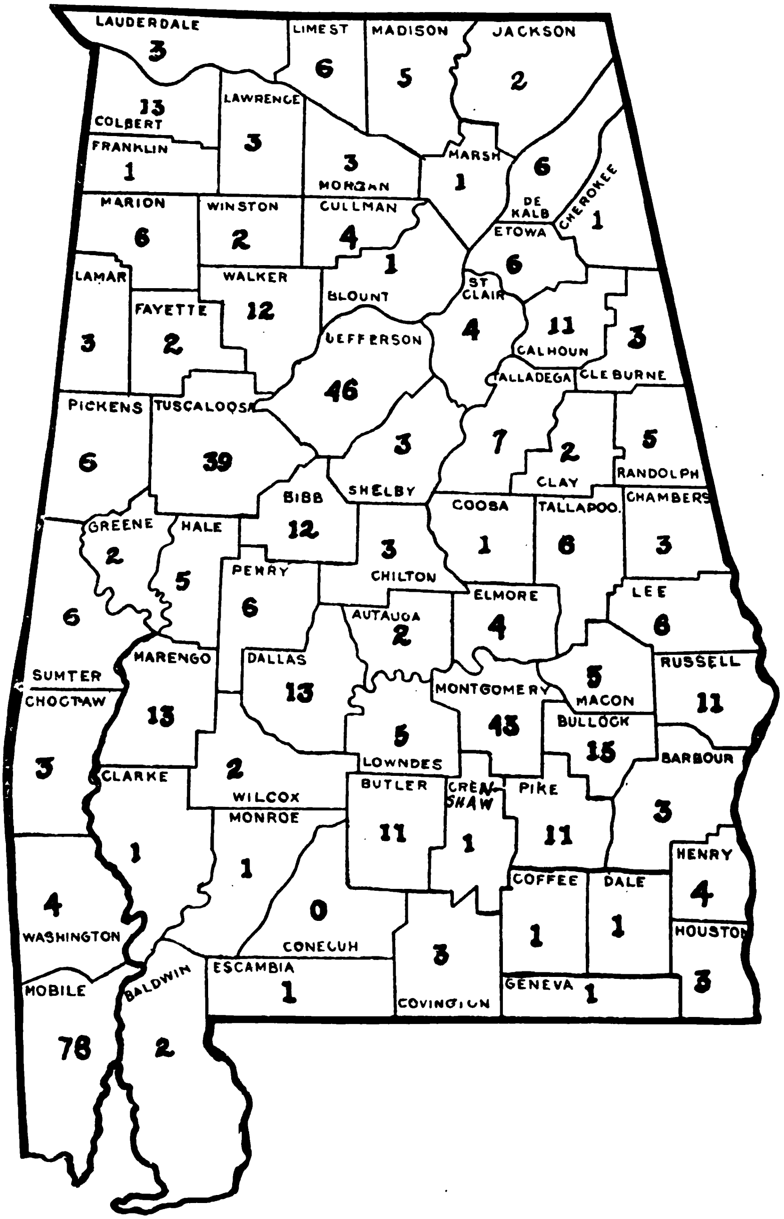
"The same doctors reporting these and physicians from other parishes, however, have estimated there are 3,588 cases in this state."

On December 4, 1915, Dr. Dowling reports the reported cases and deaths from May 1 to November 23, 1915. The cases were 970, the deaths 220. The estimated cases are 3,921.

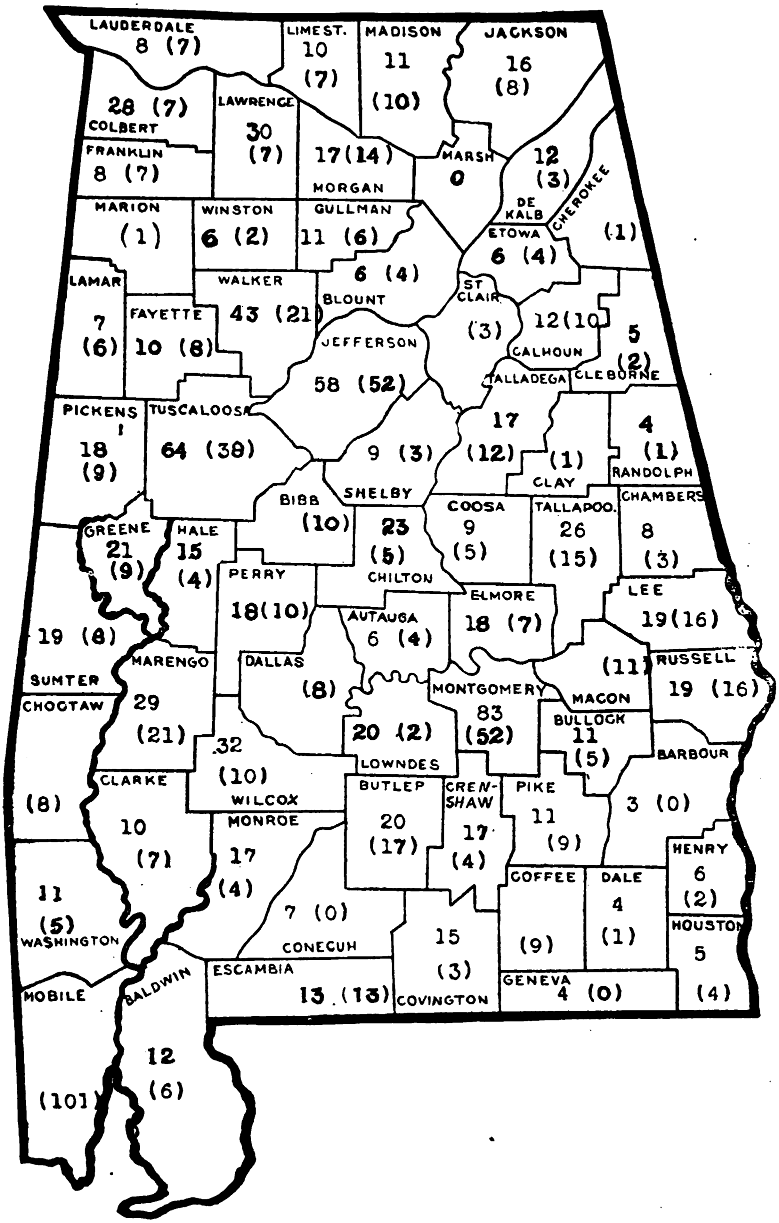
The geographical distribution of these cases is given by parishes in the accompanying outline map of Louisiana.

Virginia.

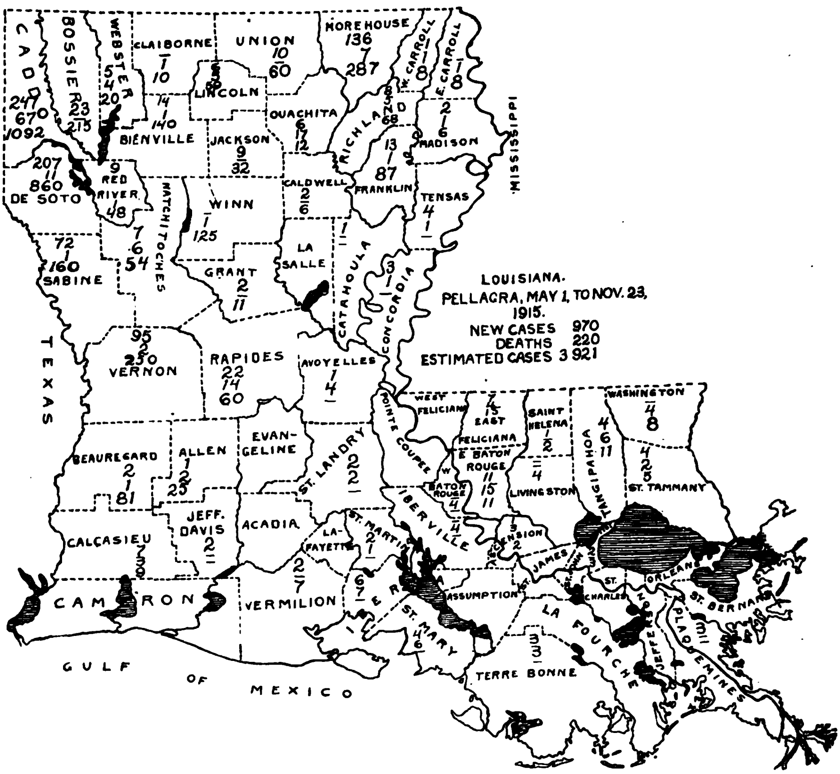
There were 564 cases of pellagra reported in Virginia from April to September, 1915. Their geographical distribution by counties is illustrated in the accompanying outline map of Virginia.



Map of Alabama showing by counties the number of deaths from Pellagra reported for 1913. Total number 500.

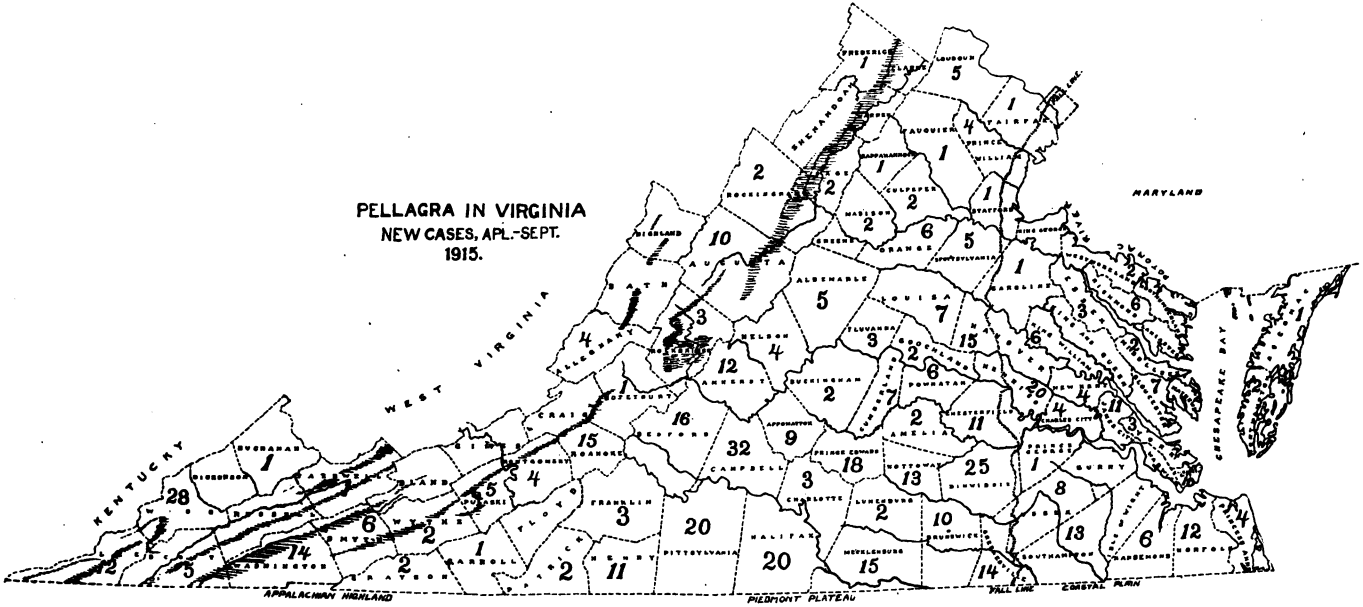


Map of Alabama showing by counties the number of cases and deaths from Pellagra reported for the first ten months of the year 1914, the latter in parenthesis, the former not.



LOUISIANA.
PELLAGRA, MAY 1, TO NOV. 23, 1915.
NEW CASES 970
DEATHS 220
ESTIMATED CASES 3 921

PELLAGRA IN VIRGINIA
NEW CASES, APL.-SEPT.
1915.



West Virginia.

Only a few cases of pellagra have been reported in West Virginia. Some of these were in the insane asylum at Weston. One or two other cases have been reported in the West Virginia Medical Journal.

Wisconsin.

Only two deaths have been reported among the inmates of public institutions. A careful survey of the state discloses only an occasional case.

New Jersey and Delaware.

The authorities of New Jersey and Delaware report that there is no pellagra in their states.

Oklahoma.

There were 151 deaths from pellagra in Oklahoma in 1915.

CHAPTER III.

GEOLOGICAL RELATIONS.

The states bordering on the Atlantic coast, and especially those from Maryland south, are divided into three geological provinces.

1. The Appalachian Mountain Province, composed of flat topped ridges separated by deep, steep-sided and flat-bottomed valleys which have been carved from folded beds of limestone, sandstone and shale of Paleozoic age.

2. The Piedmont Plateau, consisting of metamorphosed sediments of pre-Cambrian and early Paleozoic age, into which great masses of igneous rocks have been injected, the whole overlain in places by Triassic beds cut by eruptive rocks.

3. The Coastal Plain, made up of deposits from the other two provinces, much younger, consisting of unconsolidated deposits of late Mesozoic and Cenozoic age.

The Mountain Province in the states indicated, except in Virginia, is of minor area and of less interest as regards pellagra. It is not thickly settled except in the valleys and is characterized by long "limestone troughs" or valleys which extend from Vermont to Alabama. In the thickly settled limestone valleys there is enough limestone and hard water to make pellagra scarce.

The Piedmont Plateau extends from the foot of the mountains, which the name implies, eastward to the Coastal Plain. The boundary between the Piedmont Plateau and the Coastal Plain is marked by a well-defined scarp called the "Fall Line," which marks the edge of the rocks of the plateau and the beginning of the unconsolidated sands and clays of the Coastal Plain. It is so named because there are falls or rapids in all the rivers at this line. The line may be found running from Columbus, Georgia, to Augusta, Georgia, thence north across South Carolina and North Carolina, following the general trend of the mountains and the coast, across Virginia, crossing the James River at Richmond and the Potomac River at Georgetown.

In Alabama the southwestern end of the Piedmont Plateau is called the Ashland Plateau. In all the Gulf states the Coastal Plain is called the Gulf Coastal Plain.

Almost all the rocks of the Piedmont Plateau are granite or allied crystalline rocks. All the soils of the Piedmont Plateau, which are the source of the surface water supplies of springs and wells are derived from the weathering of these rocks. Such rocks on weathering can only give rise to acid clays. The small amount of alkalies originally in such rocks is washed away. The soils of the Piedmont Plateau are the residual clays, that is, they have not been transported by erosion from the original site of formation.

The soils of the Coastal Plain are sedimentary clays which have been washed down from the Piedmont Plateau. They are acid in character, and have been even more thoroughly leached than the clays of the plateau. They are the source of the surface water supplies from springs and wells of the residents of the Coastal Plain. The surface water supplies of the Piedmont Plateau are almost all what are called "freestone" or soft waters. The same is true of the waters of the Coastal Plain with a few exceptions noted below.

In the Gulf Coastal Plain there are two areas containing limestones, the Selma Chalk and the Jackson Formation crossing Mississippi and Alabama. Both of these regions are prairie and have a black calcareous soil. The black lime soil is the reason that they are prairies. They are, however, in part covered by the Lafayette Formation, a later blanket formation of clay, sand and gravel. Wherever the drinking water comes from the Selma Chalk or the Jackson Formation it is a hard or "limestone" water and the people who drink it do not have pellagra. Where the Lafayette Formation is thick enough to be the source of the surface water supply, pellagra may exist in these two otherwise immune areas.

In the southern half of the state of Missouri, northern and western Arkansas, northern Louisiana, southern Oklahoma and northern Texas are some of the oldest mountains in America. The Ozark, Boston, Oachita, Arbuckle and Wichita Mountains, while not very high, are composed of the older rocks. Their slopes and valleys are covered with clays from igneous and crystalline rocks. The whole region of their watershed is a pellagrous zone.

The region of West Tennessee between the Tennessee and Mississippi rivers is a region of sedimentary clays. It is the region of the clay industry of Tennessee. It is also the region of the greatest concentration of pellagra in Tennessee.

The states of Michigan, Indiana, Illinois and Wisconsin are more or less covered with glacial drift. This glacial drift is igneous and crystalline material transported by glaciers from the great pre-Cambrian Shield surrounding Hudson's Bay. In some parts of this region the glacial drift is deep enough to be the source of water supplies. These regions have some pellagra. Where the source of water supply goes down to the underlying limestones of this region the water is hard and there is no pellagra.

In the New England states where there is no Coastal Plain, there is some pellagra in the mountain regions and on the Piedmont Plateau which in many places comes down to the ocean.

It must not be understood that there is no clay in limestone countries. There is much clay formed from disintegrating limestone. But limestone forms so much less clay than other rocks and there is so much remaining limestone in limestone countries that the water is always hard and does not cause pellagra. The clay formed from limestones is only the clay impurity which was in the original deposit from which the limestone was formed.

CHAPTER IV.

THE CLAYS OF PELLAGROUS STATES.

The clays are not new to American geology and industry. They play a very important part in the geological reports of the southern states and are of great importance in the industries of these localities. Further to enforce the idea of their importance, their distribution and the fact that the information is at hand so as to be available to every person interested in the pellagrous area, we are going to quote from the geological surveys of the southern states the origin, classification, distribution and character of clays. We do this, first as a matter requiring explanation and the best first hand information in this discussion; second, that the information may come from the state governments of the states most interested; third, that we may state plainly to the people of the south the plain, simple means of its prevention, and the ready method of its cure.

Bulletin No. 2. The Clays of Mississippi, Mississippi State Geological Survey, 1907, gives one of the most comprehensive discussions of the formation of clays in their relation to the earth's crust. We shall quote from it first, and then follow with quotations from the geological reports of the other southern states.

The Origin of Clays.

The Lithosphere.

"The lithosphere consists of a loose mantle of earthy material, the regolith, at the surface, and a more compact, indurated substratum, the durolith, to which the term "bed rock" is often applied."

Regolith.

"The regolith consists of unconsolidated beds of sand, gravel, pebbles, bowlders and clay, or of mixtures of these together with organic matter forming loams, marls, peats and soils. The regolith varies in thickness from a few inches to several hundred feet. It is often but the residual product resulting from the weathering of the bed rock. Its thickness, therefore, may represent the amount of bed rock decay that has taken place at that point or it may represent the amount of decay that has taken place on some neighboring higher area, the debris of which has been transported to this point."

Durolith.

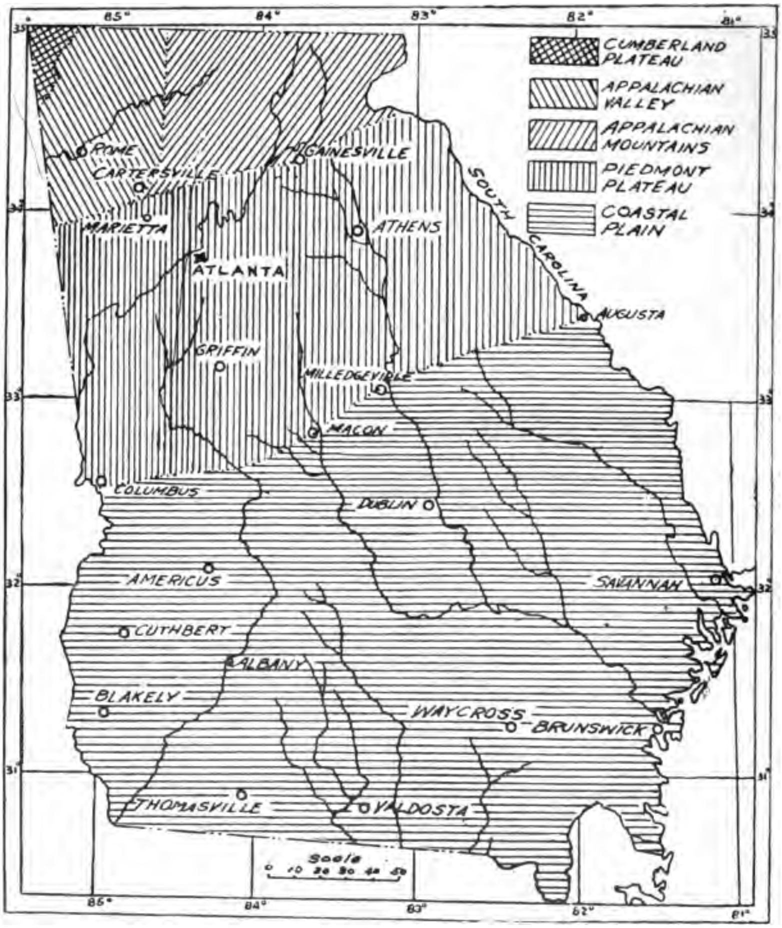
"The durolith consists of beds of consolidated and more or less indurated rocks such as shale, sandstone, limestone, coal, granite and marble. In some regions the durolith is completely covered by the regolith so that it may be studied only by means of deep cuts and the records of wells which pierce its strata. As to the thickness of the durolith we have no knowledge. The most profound excavations of nature do not descend to depths much greater than one mile. The deepest excavations or borings made by man transcend this limit only by a small degree."

Rocks of the Regolith.

"The mantle rocks are unconsolidated fragments of rock waste and organic decay forming sand, clay, marl, loess and gravels."

Clay.

"Clay is a soft rock which is usually smooth or greasy to the touch. When mixed with the proper proportion of water it may be readily molded into desired forms which will have the power of retaining their shape. This property, plasticity, is not possessed in high degree by other rocks and is therefore one of the determinative characters of clay. Clay is a mechanical mixture of minerals. The proportion of these mineral constituents may vary; hence the composition of clays varies greatly."



Physiographic Regions of Georgia.

In Bulletin No. 18, of the Geological Survey of Georgia, entitled "Second Report on the Clay Deposits of Georgia," at page 17, is the following paragraph on the origin of clays:

"All clays are of secondary origin and have been derived directly or indirectly from the decay and breaking down of the original igneous rocks of the earth's crust. This decay has taken place mainly through the atmospheric agencies, rain, frost, changes in temperature, wind, and through atmospheric gases and organic agencies, plants and animals, all of which may be included under the term *weathering*. The minerals of igneous rocks, which have been the chief source of kaolinite, or the *clay base* or *clay substance* of clays, are the feldspars."

In Bulletin No. 351, of the United States Geological Survey, entitled "The Clays of Arkansas," at page 20, is the following description of the origin of clays:

"Clays and kaolins are chiefly secondary products derived either directly or indirectly from feldspathic rocks—that is, from rocks composed either entirely or largely of the mineral feldspar, such as granite, syenite and gneiss."

In Bulletin No. 13, "Clay Deposits and Clay Industry in North Carolina," North Carolina Geological Survey, at page 11, is the following statement concerning clay:

"Kaolinite, the base of all clays, is not an original mineral of the earth's crust, but a secondary one, resulting from the decomposition of feldspars, and possibly sometimes from other aluminous minerals. The feldspars are a group of silicate minerals of rather complex composition, but orthoclase (the common feldspar), which serves as the type of the group, is a compound of silica, alumina and potash."

In Bulletin No. 1, Series IV, "A Preliminary Report on the Clays of South Carolina," South Carolina Geological Survey, at page 32, in a lengthy description of clays, the following statement is made:

"Silica occurs in clays both combined and free, and both soluble and insoluble. This mineral is in point of quantity the predominant ingredient of all clays excepting the bauxite clays. Silica represents 46.5 per cent of pure kaolinite, and in clays ordinarily constitutes the principal impurity."

Clay is generally formed by the decomposition and weathering of igneous and crystalline rocks. The crystalline rock forming the greater amount of clay on the earth's surface is feldspar. So it has been stated that clay is formed by the decomposition of feldspar. Feldspar is an important constituent of granite. In those regions of the earth where the soil is formed from disintegrated granite or other allied rocks such as pegmatite and porphyry, the soil will be clay. In countries where the limestones prevail the soils will be marls. Now the principal chemical constituent of the ingneous and crystalline rocks such as granite, porphyry and basalt is silica, and the next highest constituent is alumina. The alkalies lime, magnesia, potash and soda are present in small proportions in the hard rock. But when these rocks weather and break down, these alkalies because of being soluble, are dissolved out by rain and snow water, are conveyed in solution by small streams to the rivers and by the rivers to the ocean where they contribute to the saltiness of the ocean water and where deposited on the bottom, aid in forming limestones. This washing out of the alkalies leaves the clay consisting almost entirely of silica and alumina. The result of this is that the clay is acid. It will not support a good growth of vegetation unless an alkali is added as a fertilizer. The surface water derived from such soils and appearing in streams, springs and wells is "soft" water or "freestone" water as it is called in the southern states. This is because there is no lime or magnesia left to go into solution to make the water "hard" or "limestone" water.

The mineral or chemical composition of the igneous and crystalline rocks which break down to form clays has been the subject of much study. Several thousand analyses have been added up and averaged with the following results:

Silica	59.97	61.22	61.12	60.36	58.96
Alumina	15.39	15.75	15.77	16.07	15.99
Ferric oxid	4.03	2.71	2.69	5.48	3.37
Ferrous oxid	3.56	3.53	3.60	2.46	3.93
Magnesia	4.60	4.51	4.46	4.20	3.89
Lime	5.41	4.93	5.02	5.12	5.28
Soda	3.28	3.69	3.63	3.34	3.96
Potash	2.97	2.90	2.87	2.83	2.20
Titanium oxid	.56	.54	.61	.12	1.05
Phosforic acid	.23	.22	.23	.02	.37

As examples of the American rocks of this class the following analyses are given:

1. Watauga County, North Carolina; W. F. Hillebrand, Analyst.

2. Montgomery County, North Carolina; W. F. Hillebrand, Analyst.

3. Great Falls of Potomac, Maryland; W. F. Hillebrand, Analyst.

4. Six miles east of Ironton, Missouri; W. H. Melville, Analyst.

5. Bartow County, Georgia; H. N. Stokes, Analyst.

6. Fouche Mountains, Arkansas; H. S. Washington, Analyst.

	1.	2.	3.	4.	5.	6.
Silica	79.75	79.57	78.28	72.35	67.98	60.13
Alumina	10.47	11.41	9.96	13.78	14.84	20.03
Ferric oxid	.64	.20	1.85	1.87	1.00	2.36
Ferrous oxid	.92	.70	1.78	.36	3.15	1.33
Magnesia	.13	trace	.95	.42	.91	.76
Lime	.15	.21	1.68	.87	2.17	.87
Soda	1.36	3.46	2.73	4.44	2.66	6.30
Potash	6.01	3.52	1.35	4.49	4.76	5.97

It will be noted that these analyses are all from pellagrous regions, and that they are much lower in their percentage of lime and magnesium than the average of the several thousand analyses given just preceding them. Many of the analyses taken to make up the great average were taken from rocks much lower in silica and much higher in calcium and magnesium. They were also taken from non-pellagrous countries. In pellagrous countries as in the pellagrous areas of the United States, the lime and magnesia content of the crystalline rocks, and of the clays resulting from their disintegration is very low. That this corresponds with the alkaline content of the rocks of other pellagrous countries is evidenced by the following analyses.

1. Fabbiasco, n. Lugano; Slaytor, Analyst.
2. Angera, Lago Maggiore, Piedmont; L. Ricciardi, Analyst.
3. Invorio Superiore, Lago d'Orta, Italy; L. Ricciardi, Analyst.
4. Arona, Lago Maggiore, Piedmont; L. Ricciardi, Analyst.
5. Briga, Piedmont; L. Ricciardi, Analyst.
6. Querigut, Pyrenees, France; A. Pisani, Analyst.

	1.	2.	3.	4.	5.	6.
Silica	72.32	75.05	72.03	76.94	74.81	72.10
Alumina	13.37	13.16	14.87	12.20	13.87	15.80
Ferric oxid	.57	1.63	3.11	2.34	1.68	2.71
Ferrous oxid	2.34	3.07	2.21	....	....	....
Magnesia	3.57	.38	1.37	.32	.52	1.27
Lime	1.88	1.80	1.41	.57	1.49	1.99
Soda	2.76	.92	.78	1.47	1.46	3.10
Potash	2.50	2.58	2.32	4.65	4.68	3.12

In early geologic times many of the great inland regions of the continents were fresh or brackish water seas where a great part of the erosion of the older mountains was deposited as shale or as sandstones. The shales and their harder formations, the slates, as well as the sandstones are very silicious. While they are generally bedded between limestones, and their derived soils mixed with limestone soils, there are large areas in which the shale and sandstone soils prevail. This is especially true in certain inland areas of the United States where there are great exposures of Devonian and Carboniferous shales. Soils from these shales in the Pennsylvanian and Mississippi series of the Carboniferous are deficient in lime and are found in certain pellagrous regions in eastern Tennessee and Kentucky, southwestern Missouri and southeastern Kansas. These soils are potentially pellagrous and as they are leached and eroded, pellagra may be expected to increase in these areas.

From an examination of the analyses of the igneous and crystalline rocks it can readily be seen that if the magnesia, lime, soda and potash be washed out by water and resulting clay would be very high in silica and alumina. The oxides of iron are red and make clay yellow or red according to the amount of iron present. As to the predominance of silica and alumina all real clays agree. The analyses of three clays from the state of Georgia will be sufficient to illustrate this point:

Silica	60.24	61.36	60.70
Alumina and iron	26.72	29.04	29.24
Lime	.88	.76	.68
Water	6.28	7.46	6.74

This general condition of clays will be found to obtain in the United States where the clays have been derived from the ingneous and crystalline rocks, or from shales or sandstones, and where such soils have been leached and washed by rain and snow water, and where from the geology of the country there was no ancient inland sea, or arid region which caused the retention of the salts and alkalies. The soils will not give such an analysis where the black marls derived from limestones prevail, or in the arid intermountain regions such as the Salt Lake Valley, where the lime and alkalies have not been washed away.

The very different source of the limestone soils is contrasted with the source of the acid clays by the presentation of the following analyses of limestones:

1. Selma Chalk, Mississippi.
2. Limestone from Texas.
3. Limestone from Ohio.
4. Limestone from Indiana.
5. Cherokee Limestone, Newton County, Missouri.
6. Limestone from Kansas.

	1.	2.	3.	4.	5.	6.
Silica	8.62	.10	....	.63	....	2.56
Alumina and iron	6.60	.09	....	.39	.20	2.52
Magnesia	0.00	.18	3.08	.39	.20	.06
Lime	47.00	40.82	51.18	54.19	54.92	51.98
Water	1.00	.83	....	....	....	1.36
Carbon dioxid	36.88	32.41	42.04	44.01	43.31	41.13
Insoluble	10.00	25.57	2.12	....	1.21	....

The following partial analysis of a soil from near Salt Lake City, Utah, will illustrate this point:

Silica	19.24
Alumina	3.26
Iron oxids	1.09
Magnesia	2.75
Lime	38.94
Water	1.67
Carbon dioxid	29.57
Organic matter	2.96

A part of the silica contained in granite and similar rocks is insoluble or almost so. This insoluble silica is generally in the form of silicates or quartz. Quartz is crystalline silica and when granite disintegrates is left in the form of sand. Flint or chert is a form of silica which is not crystallized. Another portion of the silica is soluble or almost soluble so that it dissolves out of the rocks in a colloidal or jelly like condition. The more water combined with it, the more nearly liquid it is. This solution of the silica is promoted by the erosion of the soil. It has been proven that small particles of rock wear away much more rapidly when they are wet and agitated as when sand, gravel and clay are carried long distances by rain water in creeks and rivers. The silica forms a colloid with the water on the outside of small particles. This adheres to the small particles in the physical condition of a jelly, and if not agitated or abraded, prevents the formation of more of the jelly or colloid. But if abraded by contact with other particles as in the running stream, the gel is rubbed off, new surface is presented to the action of the water and new colloidal silica or gel is formed.

Colloids which go almost into solution and appear almost like water are called sol, those which are more concentrated and more of the consistency of jellies are called gel.

The above facts concerning the solubility of silica have been thoroughly worked out and proven in the reduction of ores in the great mining mills, where it is necessary to reduce ores to such a fineness that the particles will pass a sieve of 200 meshes to the inch. It has been learned that ore grinds much faster and finer when wet than when dry, due to the removal of the colloids. These same principles have been applied in the investigation of the disintegration of the feldspars used in road building, and in the mixing of clays to insure the proper plasticity and burning qualities in the ceramic industries.

The colloidal material in clays gives them their soft, greasy feel, and is the cause of their plasticity, whereby they can be molded into desired shapes and retain that shape until they are burned.

This colloidal material in suspension in water gives water a milky or opalescent appearance or color after all coarse material has settled out. This is very commonly observed in countries where the streams have their origin in clay regions.

CHAPTER V.

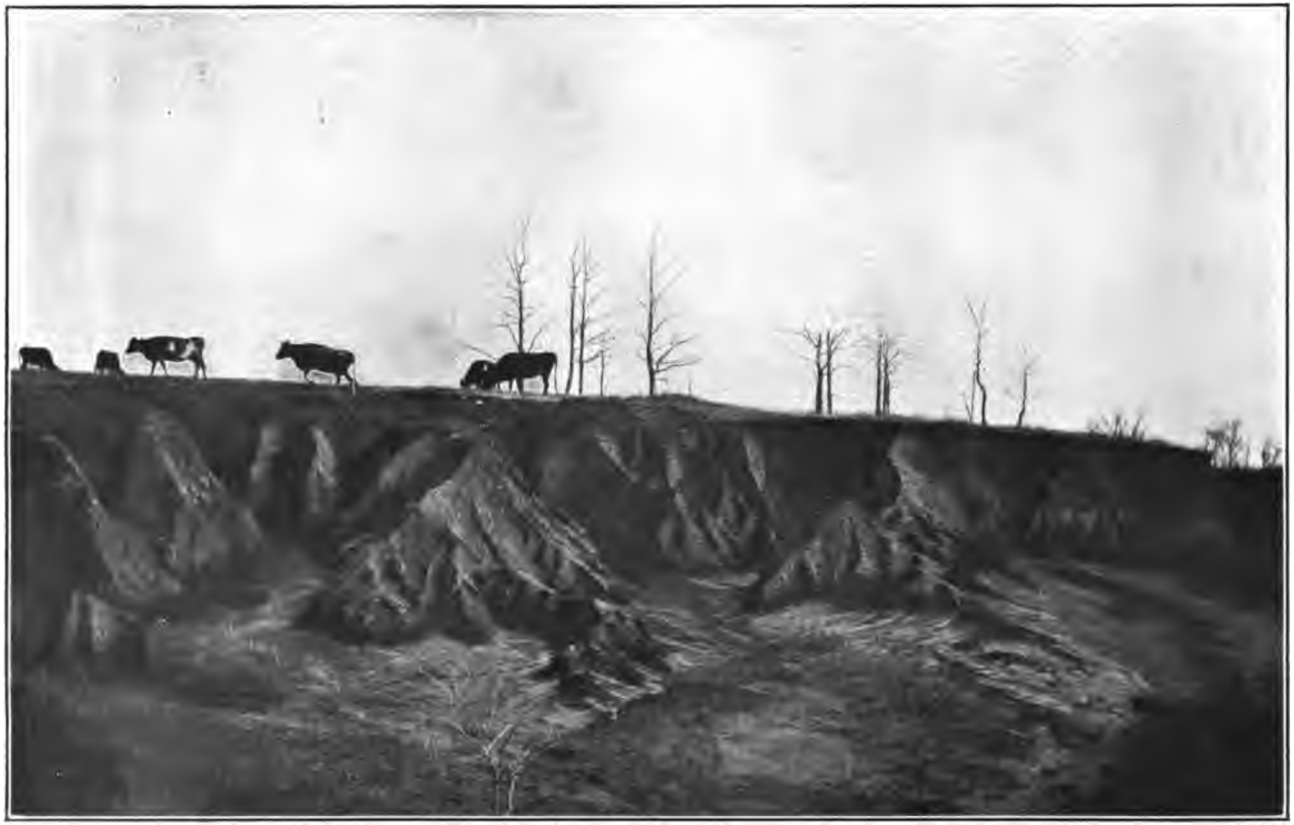
THE SOILS OF THE SOUTHERN STATES.

The soils of the southern states have been the subject of very careful study by the United States Bureau of Soils. A resume of a few of the most common types in the farming region of the south will show why there is clay in the surface waters. These soils are divided into series and described as such. The series selected for description are from the Piedmont Plateau and Coastal Plain Provinces where pellagra is found. The soils of the Delta regions where there is no pellagra are not described.

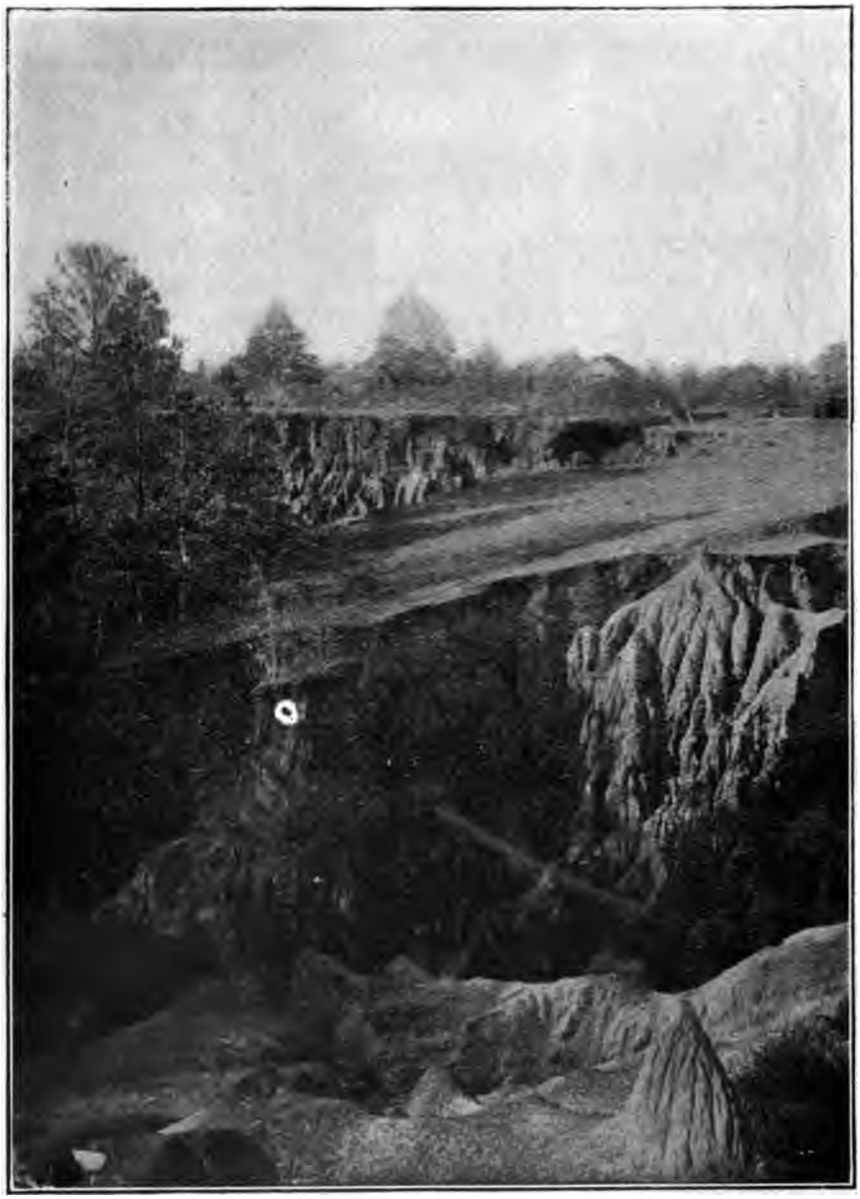
1. Cecil Series:

The Cecil series includes the most important and widely distributed soils of the Piedmont Plateau. The heavier members are known as the "red clay lands." These soils are characterized by their red clay subsoils and gray to red soils ranging in texture from sand to clay, the lighter colors prevailing in the sandy members. A characteristic of the subsoil is the content of sharp quartz sand and the frequent occurrence of veins of quartz. Mica flakes are also usually present in the subsoil. The soils are of residual origin and derived principally from granite and gneiss, weathered to great depths, so that rock outcrops are rare. Fragments and boulders of the parent rock are, however, found in place on the surface. The topography is rolling to hilly, with level to undulating areas in situations where stream erosion has not been active.

Soil Survey of Forsyth County, North Carolina, October 31, 1914.



Erosion of Lafayette Formation—Bulletin 71. Bureau of Soils.



Erosion of Surface Loam and Lafayette Formation, Near Rocky Springs, Miss. Bulletin 71, Bureau of Soils.

2. Durham Series:

The Durham series is characterized by the grayish color of the surface soils and the yellow color of the subsoil. The soils are derived from light-colored, rather coarse-grained granite and gneiss, consisting principally of quartz and feldspar, with some mica. The topography is generally gently rolling and the drainage thorough or in places excessive, owing to the sandy, porous texture of the subsoil. These soils occur in the Piedmont region from Virginia southward to Alabama.

3. Appling Series:

The types of the Appling series are characterized by the grayish to pale yellow color of the surface soils and the mottled or streaked red and yellow color of the subsoils. In places the color varies from yellow to red, while grayish colors are also occasionally noted in the subsoil. These soils are derived principally from schist of grayish color and undetermined composition, from hornblende schist and from gneiss. The Appling series is a Piedmont series encountered so far only in the Carolinas and Georgia.

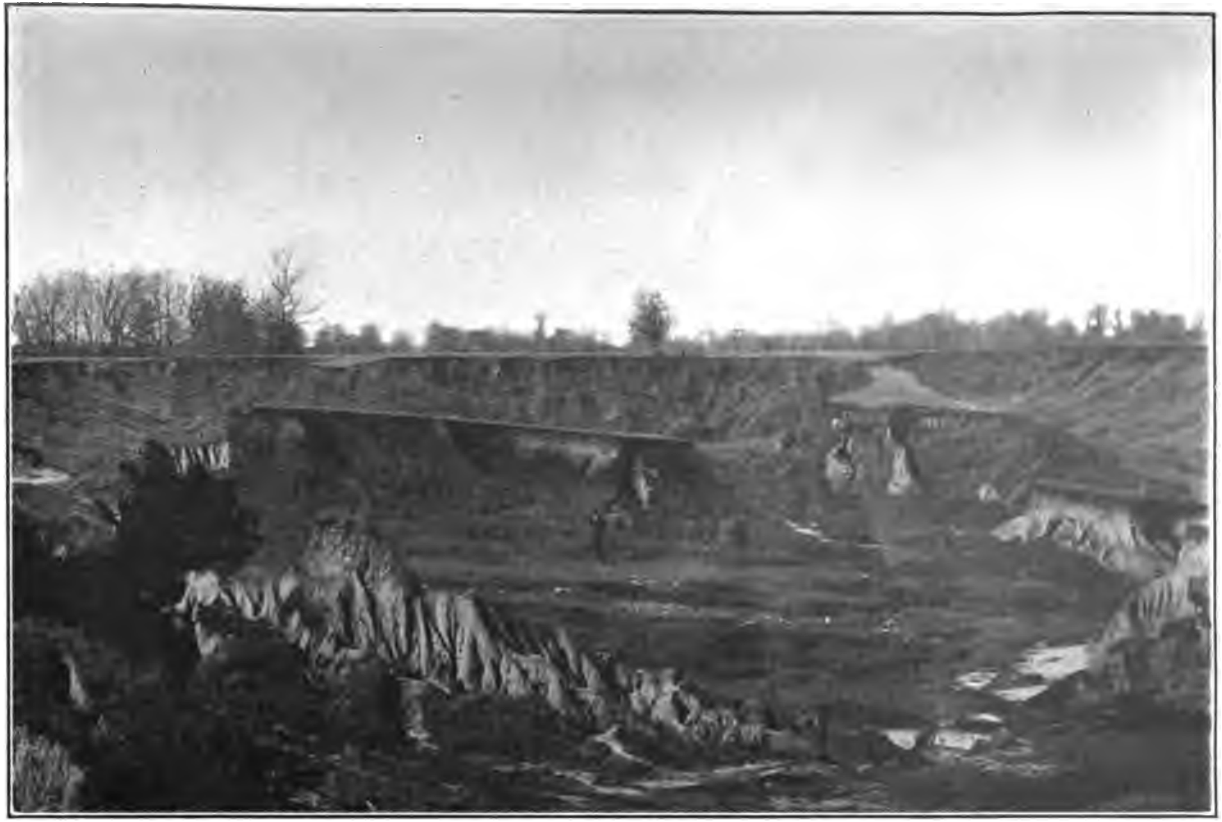
4. Iredell Series:

The soils of the Iredell series are light brown to almost black in color and frequently carry small iron concretions. The subsoils consist of extremely plastic, sticky, or waxy clay of a yellowish-brown to greenish-yellow color. Disintegrated rock is very often encountered within the three-foot section. The topography varies from nearly flat to gently rolling. The parent rocks consist mainly of diorite, hornblende schist or hornbelnde gneiss and chloritic rocks.

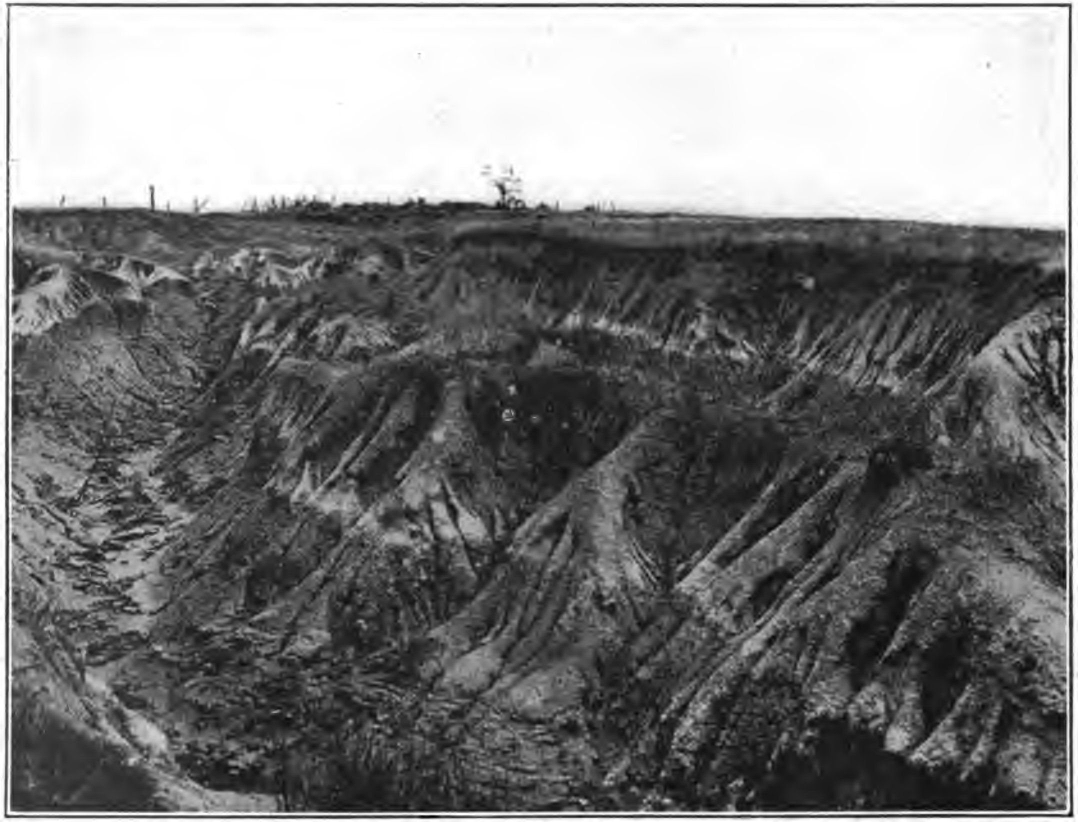
5. Norfolk Series:

The surface soils of the Norfolk series are prevailing gray, ranging from light gray to grayish-yellow. The subsoils are yellow and have a friable structure. These soils occupy nearly level to rolling uplands throughout the Atlantic and Gulf Coastal Plain. They are derived mainly from Piedmont-Appalachian material.

Soil Survey of Bamberg County, North Cerolina, September 18, 1914.



Erosion of Lafayette Formation Near Yzaoo City, Miss. Bulletin 71. Bureau of Soils.



Gullying of Abandoned Field, Near Grand Junction, Tenn. Bulletin 71. Bureau of Soils.

6. Orangeburg Series:

The Orangeburg soils are predominantly gray, ranging to reddish brown. The soils are open structured, and the subsoils consist of friable sandy clay. This series is confined to the uplands of the Atlantic and Gulf Coastal Plain, being most extensively developed in a belt extending from southern North Carolina to central Texas. The materials forming the soils were originally washed from the Piedmont and Appalachian regions.

7. Tifton Series:

The Tifton soils are prevailingly gray, ranging to brownish gray. The subsoils consist of bright yellow, friable sandy clay. Small iron concretions occur on the surface and throughout the soil section. The topography varies from flat to gently rolling, and drainage is good. The Tifton series extends through southern South Carolina across Georgia into Alabama. The soils are sedimentary from the sandy clays of the Coastal Plain region.

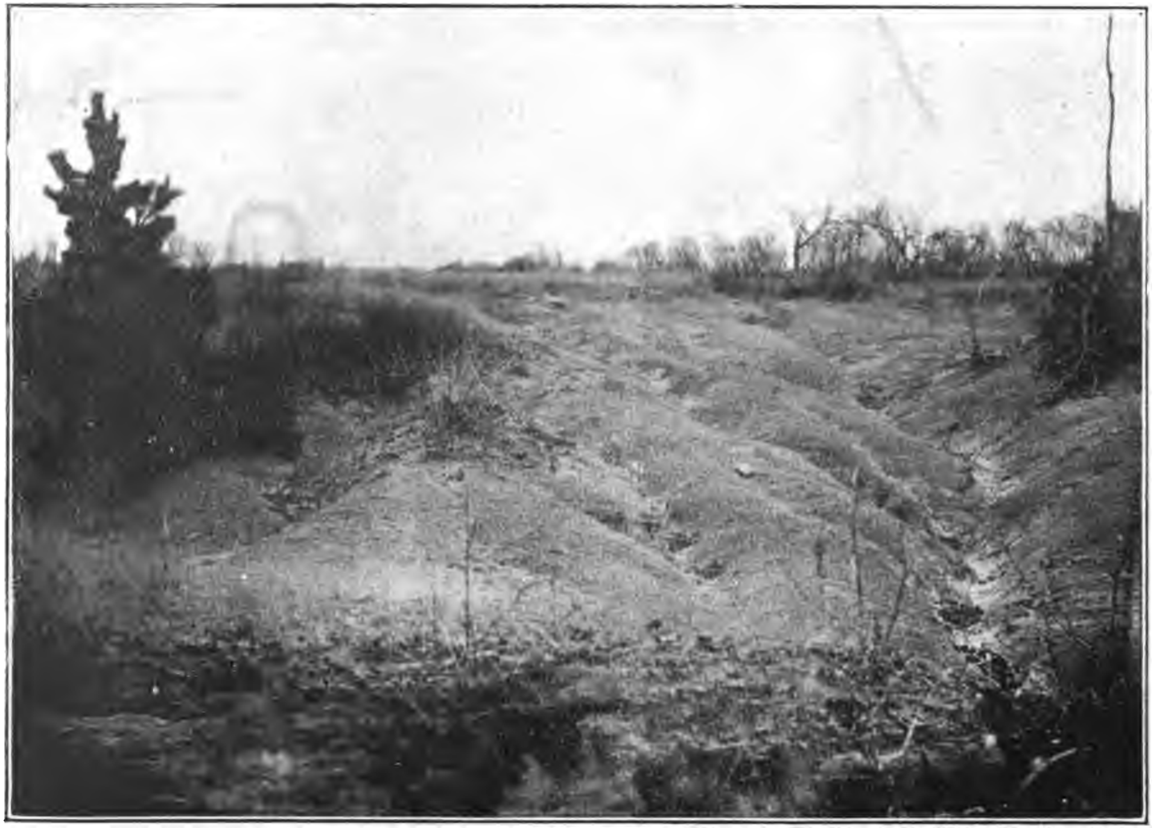
8. Susquehanna Series:

The Susquehanna soils are gray, ranging to reddish. The subsoils are mottled gray and red or gray, red, and yellow, and consist of plastic, heavy clay. The color of the subsoil varies, often being red, white, drab, yellow, and sometimes purple, although red practically always predominates, the other colors appearing only as mottlings in the lower part of the section. The Susquehanna series is most extensively developed in the higher part of the Coastal Plain from the vicinity of Chesapeake Bay to central Texas.

Soil Survey of Jones County, Georgia, December 31, 1914.

9. Ruston Series.

The Ruston soils are gray, ranging to grayish brown. The subsoils are reddish yellow to yellowish red or dull red and are moderately friable, consisting generally of sandy clay. Occasionally the lower subsoils are mottled with gray and shades



Gullying of Abandoned Field, Near Oxford, Ga. Bulletin 71. Bureau of Soils.

of yellow. This series is intermediate between the Orangeburg and Norfolk on the one hand and the Susquehanna on the other in point of subsoil structure. The Ruston soils are closely associated with the Orangeburg and Susquehanna. They are sedimentary in origin.

There are a number of other soils listed and described in the southern states, some from the mountain sides and others from the swamps. They are not important in this discussion.

Prairie Soils.

In Bulletin No. 8, of the Mississippi State Geological Survey, "A Preliminary Study of the Soils of Mississippi," at page 61, the following significant paragraphs appear:

Black Prairie Belt. Lying immediately to the west of the region of hills just described (Tennessee River Hills) is a broad low-lying belt of land of slight relief. In all its characters this region is the antipode of the other. Its surface is not only nearly level, but consists of open prairies almost devoid of tree growth, but having a rich herbaceous flora of prairie loving species, like the prairie clovers, mellilotus, compass plants and milk weed, besides abundance of good grasses.

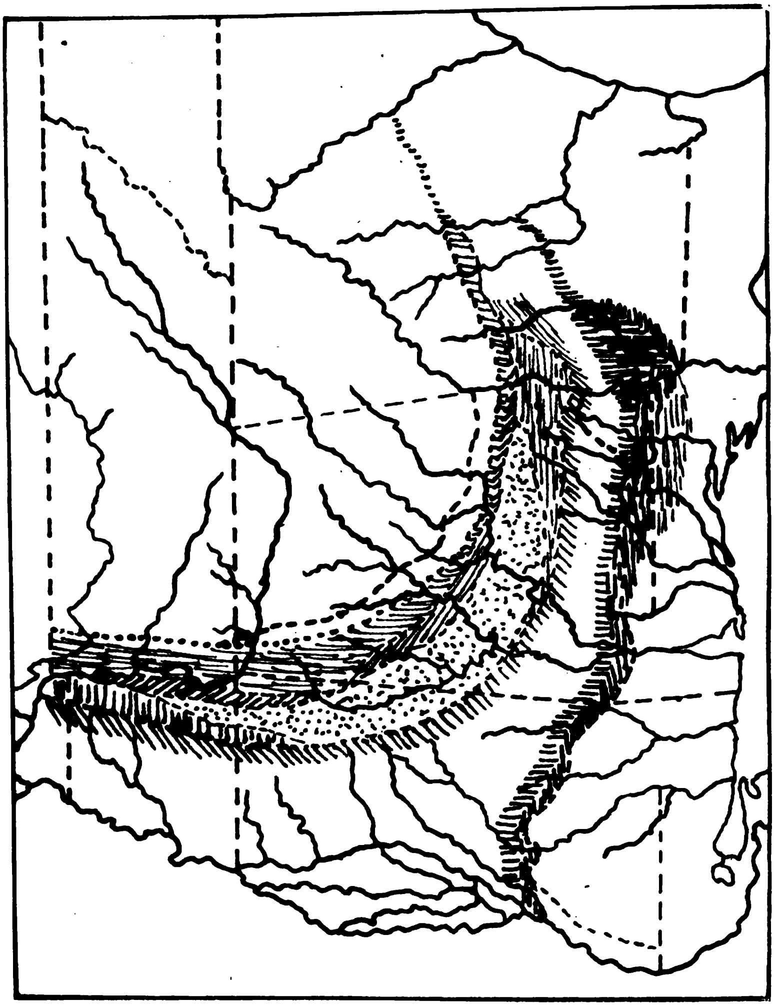
The soils are black calcareous clay loams, that do not, in the flatter areas, drain perfectly, but are very strong and productive.

This whole region marks the outcrop of the Selma Chalk or Rotten Limestone of the Cretaceous, which forms the bedrock from which the black prairie soils are derived. The region is one of fine farms, prosperous towns and rapidly growing wealth.

At page 64 of the same Bulletin the following appears:

Jackson Prairie Belt.

The characteristic soil is a black calcareous prairie soil, very similar to that of the Cretaceous prairies, though the prevailing soil of the area in the western part is the brown loam already described. The soils are very rich and the region is one of the most prosperous in the state.



Cretaceous and Tertiary Prairies in Mississippi and Alabama.

The geological formation underlying this region is the Jackson, consisting of calcareous clays, marls and soft limestones.

"Black Prairies" of Texas.

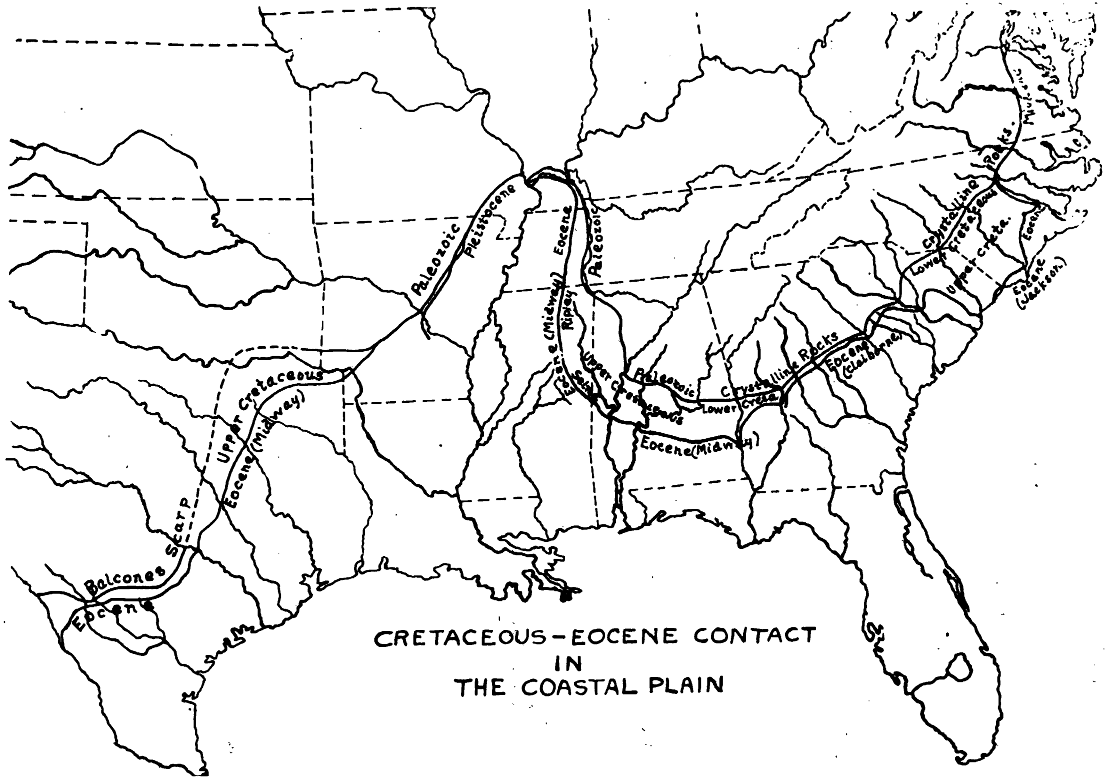
In the Cretaceous area in Texas there is an extensive region called the "Black Prairies." The soils of these prairies are alkaline, and are derived from strata of rock similar to the Selma Chalk. They form one of the richest agricultural belts of Texas. The drinking waters derived from these areas contain carbonates of lime and magnesia. These regions are not pellagrous. In places in this black prairie region, as in Alabama and Mississippi, deep wells have been sunk through the limestone strata into the sands and clays of older strata below in search of soft or freestone water. Where such water has been secured, pellagra may be found.

The soils of the black prairies of Texas are described in the Soil Survey of the Paris Area; Soil Survey of Robertson County; Soil Survey of Bastrop County, Texas; Bureau of Soils, Department of Agriculture, Washington, D. C.

In the Reconnoisance Soil Survey of Western Kansas, U. S. Bureau of Soils, March 29, 1912, the following statement is made:

Alkali.

In all arid and semi-arid regions soluble salts are released from disintegrating rocks faster than they can be removed by leaching with the limited amount of water, and there is danger in some localities where conditions are favorable that alkali may be concentrated in amounts dangerous to plant growth. In western Kansas this takes place only where drainage is restricted and there is great evaporation and concentration or on irrigated land where the capillary movement of soil water accelerates the accumulation. Where water passes through the soil it takes a portion of the soluble material into solution, and when the water is brought to the surface and evaporated the salts are left behind. The latter process has caused a concentration of alkali on the irrigated land, particularly in the Arkansas Valley.



CRETACEOUS-EOCENE CONTACT
IN
THE COASTAL PLAIN

In this connection again we desire to call attention to the fact that prairie soils are calcareous and contain alkalies to such a percentage that trees will not grow, that calcareous soils of low alkalinity produce the hardwood species such as the oaks, that acid silicious soils produce pines and that on the sandy hillsides and mountains the chestnut grows. Chestnut will not grow on a limestone soil.

Pellagra does not grow on these prairie limestone soils any better than timber. Pellagra, besides having the same distribution as clay soils, has the same distribution as pine timber.

The "glacial drift" of certain northern states heretofore mentioned has weathered into clays. The surface soils do not effervesce with hydrochloric acid, that is, they contain no alkali. Watery solutions turn blue litmus red, that is, they are acid. The soils of this region are principally of the Miami and Coloma Series. Much of this region was formerly heavily covered with pine timber.

The soils of the Coastal Plain, the Piedmont Plateau, the Limestone Valleys and the Glacial and Loessial Provinces have been analyzed. The results of some of these analyses are given in the following table.

	Coastal Plain Province.		Limestone Valley and Upland Province.			
SiO_2	94.50	85.30	79.35	74.81	70.99	66.49
Al_2O_3	2.07	8.82	8.89	12.80	11.39	14.80
Fe_2O_3	.83	1.91	4.44	5.28	4.28	5.99
CaO	.39	.38	.63	.40	.93	.35
MgO	.09	.19	.39	.33	1.08	1.93
K_2O	.10	.12	.67	.75	2.71	3.58
Na_2O	.11	.07	.24	.16	.82	.66

	Piedmont Plateau Province.								
SiO_2	66.49	44.15	88.57	55.69	80.79	69.35	76.71	74.38	84.58
Al_2O_3	17.11	27.58	5.76	24.42	10.55	18.04	12.85	16.31	5.54
Fe_2O_3	7.43	16.23	1.55	8.83	1.61	3.24	2.81	2.56	3.30
CaO	.36	.44	.39	.40	.89	.72	.08	.21	.21
MgO	.31	.09	.21	.29	.19	.29	.29	.38	.25
K_2O	.62	.61	.82	1.06	3.96	3.34	3.26	4.07	.74
Na_2O	.16	.15	.16	.14	.87	.89	.39	.39	.14

Glacial and Loessial Province.

SiO_2	75.12	74.64	73.61	71.43	65.68	73.80	73.50	76.86
Al_2O_3	10.49	12.26	9.67	13.44	14.15	13.24	9.10	9.49
Fe_2O_3	4.13	5.01	3.54	4.28	5.67	4.37	4.30	3.79
CaO	.49	.37	1.08	1.40	1.36	1.19	.94	.93
MgO	.48	.90	.77	1.28	.83	.39	.71	.58
K_2O	1.40	1.99	2.28	2.03	2.16	2.22	2.03	1.04
Na_2O	.90	.99	1.03	.63	1.39	1.75	1.67	1.22

It will be noted that silica is very high in the Coastal Plain Province and that all the alkalies are very low, that in the Piedmont Plateau there is a slight increase in alkalinity, and another slight increase in some analyses from the Limestone Valleys. The greater number from the Glacial Province show an appreciable increase in alkalinity. This slight increase in alkalinity is the measure of the difference between pellagrous and almost immune regions.

The Coastal Plain soils extend from Texas to Long Island. They are all low in alkalies as appears in the following table:

	CaO %	MgO %	K_2O %
Collington sandy loam, New Jersey	0.12	0.13	0.79
Norfolk sand, Maryland	.18	.19	.60
Norfolk loam, Maryland	.24	.10	.79
Leonardtown loam, Maryland	.07	.29	1.11
Orangebury sandy loam, Alabama	.08	.05	.28
Crowley silt loam, Louisiana	.19	.29	.92
Orangeburg fine sandy loam, Texas	.14	.10	.42

Soils derived from the disintegration of limestones and shales differ very much in their alkaline content, depending upon whether the limestones or shales predominate in their constituents. The following four partial analyses show this difference.

	CaO %	MgO %	K_2O %
Oswego silt loam, Kansas	0.40	0.36	1.24
Hagerstown loam, Tennessee	.40	.56	.77
Hagerstown clay, Kentucky	3.12	1.54	4.30
Houston clay, Alabama	28.02	1.21	1.01

The shale types of soils are sometimes very low in alkalies. A very striking example is the Oswego Series, in Kansas, given just above. It is largely derived from the Cherokee Shales, which in southeastern Kansas average about 500 feet in thickness. Cherokee County, Kansas, is a pellagrous focus, 15 cases being reported from the city of Galena in 1915.

CHAPTER VI.

THE WATER OF PELLAGROUS AREAS.

So many factors enter into the chemistry of water supplies that the definition of a pellagrous water is difficult. From all the chemical and clinical data at hand, it seems to consist in the presence of colloidal silica and a lack of alkaline carbonates. As this discrepancy may exist in every degree, and may vary in each water supply with the rainfall and water consumption, it is evident that the toxic character of a water supply may vary from nil to very toxic. Chemical, laboratory and clinical experience also indicate that the chlorids and sulfates in drinking water add to its toxic character if carbonates be absent. As great numbers of the population of the pellagrous states are supplied by waters obtained from all sources, the waters of pellagrous areas must be considered as surface waters, ground waters and deep waters.

Surface Waters.

Surface waters are composed of the "run off" from rain and snow. The amount of run off from any area depends upon the precipitation, topography, cover and permeability of the soil. Surface water finally finds its way into the small streams and then into the rivers. Where there is plenty of cover and the topography is not precipitous, there is little erosion and the water does not contain much silt or clay. Where the fields are plowed, not protected from erosion and there is considerable slope, the water contains much wash from the soil.

These waters dissolve and leach out the soluble salts from the soil and transport them in solution to the rivers and to the ocean. Rivers in a considerable course accumulate more of the alkalies than can generally be found in springs, ponds or shallow wells of the same locality. Each particle of water in a flowing stream can come in contact with and put into solution more of any soluble substance than a like particle of standing water. Then long rivers may pass through alkaline areas in their course and become more alkaline than other areas in their lower watershed. For these reasons, many cities taking their water supplies from great rivers are not pellagrous although situated in very pellagrous areas. All the population using the municipal water supply may be getting an alkaline water, while the people in the surrounding country, or those depending upon wells and springs in the suburbs may be using a silicious soft or "freestone water, and be subject to pellagra." The surface waters as exemplified by the rivers, show plainly the difference in their watersheds. Those wholly within the pellagrous area are very low in alkalies. Those crossing the great plains or wholly within the non-pellagrous areas are much higher in alkalies. Some alkaline rivers invade the pellagrous area and become the source of the public water supplies of cities, thus making immune the city population of an otherwise highly pellagrous area. A conspicuous example is the Arkansas River supplying the water of Little Rock, Ark.

Many of these rivers have been sampled daily from six months to a year and their waters submitted to chemical analysis.. We have selected a number of both classes for the purpose of comparing their silica, calcium and alkalinity, and have arranged them in the following table:

Rivers of the Pellagrous Area.

River	Location	Silica SiO₂	Calcium Ca.	Bicarbonate Radicle HCO₃
Alabama	Selma, Alabama	21	18	48
Cahaba	Birmingham, Ala	16	13	52
Cape Fear	Wilmington, N. Car	9.9	5	25
Chattahoochee	West Point, Ga.	20	4.8	23
Dan	South Boston, Va.	24	5.6	33
Flint	Albany, Ga.	24	8.8	31
James	Richmond, Va.	18	14	60
Neuse	Raleigh, N. Car	26	5.9	35
Oconee	Dublin, Ga.	21	8.5	37
Ocmulgee	Macon, Ga.	26	6.3	28
Oostanaula	Rome, Ga.	24	12	52
Pearl	Jackson, Miss.	18	7.1	32
Pedee	Pedee, N. Car.	26	6.9	32
Potomac	Cumberland, Md.	8.2	24	36
Roanoke	Randolph, Va.	21	9.5	53
Savannah	Augusta, Ga.	23	5.7	30
Tombigbee	Epes, Ala.	25	18	67
Wateree	Camden, S. Car	25	6.3	34

In the less pellagrous areas of Tennessee and Kentucky, where the soils are partly derived from Devonian Shales and sandstones and from the shales of the Mississippian and Pennsylvanian series of the Carboniferous, the waters of the rivers are slightly more alkaline.

River	Location	Silica SiO₂	Calcium Ca.	Bicarbonate Radicle HCO₃
Cumberland	Nashville, Tenn.	20	26	92
Cumberland	Kuttawa, Ky.	18	28	100
Kentucky	Frankfort, Ky.	16	21	78
Tennessee	Knoxville, Tenn.	25	22	86
Tennessee	Gilbertsville, Ky.	20	19	72

Alkaline Rivers.

River	Location	Silica SiO₂	Calcium Ca.	Bicarbonate Radicle HCO₃
Arkansas	Little Rock, Ark.	28	55	148
Brazos	Waco, Texas	22	121	158
Cedar	Cedar Rapids, Ia.	14	48	209
Colorado	Austin, Texas	18	52	195
Des Moines	Keosauqua, Ia.	22	58	216
Grand	Grand Rapids, Mich	14	56	214
Iowa	Iowa City, Ia	19	49	210
Kalamazoo	Kalamazoo, Mich.	17	55	216
Maumee	Toledo, Ohio	17	57	173
Miami	Dayton, Ohio	17	59	244
Minnesota	Shakopee, Minn.	23	82	296
Mississippi	Minneapolis, Minn.	15	40	188
Missouri	Florence, Neb.	31	65	203
Platte	Columbus, Neb.	32	63	186
Red	Shreveport, La.	30	74	135
Rio Grande	Laredo, Texas	29	104	178
Shenandoah	Millville, W. Va.	15	32	132
Wabash	Logansport, Ind.	14	82	234
E. Fork White	Azalia, Ind.	15	61	276
W. Fork White	Indianapolis, Ind.	14	74	291

The country people in pellagrous areas depend largely upon springs and shallow wells for their supply of drinking water. These wells and springs vary in their mineral content just as the strata from which they are derived. In certain Cretaceous areas as the Selma Chalk in Alabama and Mississippi, hard water may be found. Where these same limestone areas are overlaid by the Lafayette and Grand Gulf formations to a depth of 50 feet or more, the surface clays, sands and gravel are the source of surface water and the shallow wells and springs are soft water. There can be no rule which can be applied to the whole region. The rule of hard or soft water can only be applied in each individual case. A number of shallow, or small common springs, which are the type of many hundreds or thousands supplying the country people, give the following analyses:

Silica	25.50	34.40	30.20	38.60	39.42
Alumina and Iron	1.50	12.40	5.80	1.10	1.25
Chlorin	5.10	6.12	6.30	5.25	6.30
Lime	4.90	4.30	7.00	9.10	10.31
Magnesia	3.00	3.75	4.60	3.86	4.05
Soda	9.50	14.84	4.70	12.30	13.05
Potash	4.00	3.52	3.45	3.04	2.45
Sulfuric acid	5.60	8.24	3.50	9.28	1.20

Typical shallow wells in the pellagrous area show a high silica content. As in the springs, when there is a high sodium, there is also a high chlorin or sulfuric acid, thereby making the water more pellagrogenic than if the silica alone predominated. A number of such analyses of shallow wells is here given:

Silica	10.8	10.8	17.7	19.6	17.2	27.8
Alumina and Iron	.8	8.9	15.4	11.6	2.6	2.5
Chlorin	3.5	.8	3.1	4.1	10.5	38.4
Calcium	2.8	4.5	7.0	8.2	11.9	12.3
Magnesium	1.0	3.0	.3	.3	2.2	2.6
Sodium	3.7	2.6	8.1	6.6	24.6	51.8
Potassium	.9	1.3	4.3	3.0	7.6	3.9
Sulfuric acid	2.1	15.4	5.2	5.8	5.1	5.0

In parts of the pellagrous area the surface water is insufficient or unsatisfactory. Many artesian or deep wells are sunk to a sufficient or satisfactory supply. Many of these are high in silica and low in alkaline carbonates.

Silica	97.10	43.10	83.43	56.7	35.4
Alumina and Iron	16.56	5.00	33.81	3.3	3.4
Chlorin	12.20	6.80	10.20	5.4	.7
Lime	5.50	2.12	48.31	39.0	276.3
Magnesia	1.19	1.28	11.75	19.2	122.9
Soda	17.79	3.95	15.75	5.5	41.3
Potash	5.33	3.32	5.56	.3	....
Sulfuric acid	1.34	2.86	2.16	5.4	1071.5

A large number of wells are in the class of the last of the above series. It will be noted that the calcium and magnesium of this water must be sulfates, which add to the intoxication of the silica and do not have the neutralizing action of the carbonates.

Other wells in the limestone valleys of the mountains, and in the narrow limestone areas of the Cretaceous and Tertiary are low in silica and have a controlling amount of calcium and magnesium carbonate, and could not produce the pellagrous intoxication.

Silica	15.50	11.45	13.00
Alumina and Iron	6.06	2.94	1.80
Chlorin	7.00	5.60	4.70
Lime	87.12	62.38	80.40
Magnesia	3.31	1.85	5.14
Soda	4.84	4.27	12.40
Potash	2.12	1.73	3.55
Sulfuric acid	3.06	3.68	9.14

Throughout this work we have frequently had occasion to refer to the Lafayette formation as a source of supply of drinking water even in the limestone regions such as the Selma Chalk. In this connection we desire to quote from the Underground Water Resources of Alabama, of the Geological Survey of Alabama, at page 143, describing the origin of shallow waters in Greene County.

"The Tuscaloosa formation underlies a small area, about one township in extent, in the northeast corner of Greene County; the rest of the county is underlain by beds of the Eutaw and Selma chalk in belts of nearly equal width from northeast to southwest. Over all the older rocks was spread the Lafayette mantle of pebbles and red loam, remnants of which are still to be seen in the high plateaus between the water courses, where the country has been least affected by erosion. These high, level lands, 400 to 500 feet above tide, are excellent farming tracts. The soils are slightly less fertile than those of the prairies, but their level surface, their responsiveness to fertilizers, and the abundant supply of the best freestone water, stored up in the pebbles and sands and easily reached by wells less than 100 feet deep or appearing as hillside springs, more than compensates for the slight difference in original fertility."

CHAPTER VII.

COLLOIDS.

The study of pellagra is inseparable from a study of the colloids. Organic chemistry and the chemistry of organic intoxications in the last few years has developed largely into a study of the colloids. Agriculture and certain manufacturing and construction industries have lent much force to this investigation. Especially is this true in the study of soils in agricultural experiment stations, the study of colloidal dyes in manufacturing industries dealing with the coloring of textile fabrics, the study of the plasticity of clays resulting from colloids in the ceramic industries, and the study of the colloids of Portland cement both in its manufacture and in its use in building construction.

Medicine, especially in America, is generally the last to take up anything new. Nevertheless, the chemistry of the colloids marks an epoch of progress in pharmacology, in that in the Lloyd Laboratories in Cincinnati, it has been proven that a colloidal silicate of alumina by a process of colloidal absorption is able to remove the bitter from alkaloids and the nauseating properties from ipecac and emetin without altering their chemical or therapeutic strength or value. This largely depends upon that fact that certain compounds with colloids are insoluble either in acids or alkalies, and carry over their properties until they reach a medium in which they are soluble. Happily these principles apply in pellagra.

All the tissues of the animal and vegetable kingdoms are colloids. In vital, normal, functioning organic structure, nature does not tolerate crystallization. The different colloids of animal structure owe their consistence to aggregation, coagulation and precipitation which accomplishes an extrusion of water, and their softness and fluidity to the presence of greater or less amounts of ionized water. All the combinations of digestion, assimilation, absorption, katalysis and elimination are colloidal combinations. They are never the quick, violent, heat producing and explosive combinations of the chemical laboratory, producing corrosions, boiling, and complete change in the nature of substances. Tissue and function could not tolerate such action. The chemical operations of organic life are the slow partial changes of aggregation, coagulation, hydrolysis, adsorption, association, dissociation, dialysis, the reactions accomplished by the intervention of ferments and enzymes, the slow processes of oxidation; all accomplished by ionic action between substances of ions having opposite electronic charges, and at temperatures within the range of the temperatures of living plants and cold blooded animals up to the temperature of the birds. The chemical action of the colloids tends rather to equilibrium than to complete change and can be satisfactorily and completely accomplished at comparatively low temperatures. Sharks and alligators have a ravenous appetite, and as good a digestion as the ostrich, but they require more time. This is true of all colloidal reactions.

All substances required in the vegetable and animal economy are found in the colloidal state. This does not mean that they are always in the colloidal state, but that all such substances have a colloidal form as distinguished from a crystalline form. From this we have come to understand that substances considered insoluble, inert and incapable of absorption, are really soluble at least to the liquid colloid form or sol; that as such they fulfill the very requisities of animal and vegetable absorption, and may be utilized to nourish and build tissue, or if noxious, may intoxicate and even kill.

Now colloids are substances which do not crystallize, and may be of all consistencies from that of a watery sol to the hard glass of the window pane. The soft colloids carry more ionized water than the solid colloids. These physical conditions are called phases of the colloid. The watery colloid or sol is in the dispersed phase, that is, it has the maximum separation of substances because of the presence of much ionized water. When for any reason, such as evaporation, or increased evaporation because of increased temperature, or aggregation, coagulation or precipitation, or the coagulating or deflocculating action of electrolytes, water is extruded or substituted or expelled from the colloid, it changes into a less dispersed phase.

At the initiation of animal or vegetable life the colloids of the tissues are at their maximum viable dispersion. As life advances, water is slowly but progressively lost. This rapidity of the loss of water is a specific characteristic of the tissue of the plant or animal concerned. When the loss, extrusion or substitution of water, and the concomitant concentration of the protoplasm of tissue reaches such a point that the cell is no longer capable of division, natural death ensues. The trajectory of life is indigenous and specific for every tissue. It may be measured in the few minutes of life of the microscopic organism, or in the centuries of the life of the giant redwood, but at the end it fails from lack of ionized water. In the natural physiology, the extrusion of water from the colloids and the aggregation, coagulation and precipitation of colloids is the mechanism of senility which ultimately resutls in natural death.

With proper nutrition, assimilation and elimination, the human organism maintains a colloidal equilibrium within the limits of living protoplasm from fifty to even 100 years. This equilibrium is an alkalinity which is measured by 0.85 per cent of sodium chlorid. This is called the physiological or isotonic condition. A condition of hypoalkalinity, sometimes erroneously called acidity, tends to ulceration, hemolysis, anemia and degeneration; a condition of hyperalkalinity tends to the manifestations of senility and neoplastic growth. The aged human body presents a concentration of colloids, a lack of water, with the consequent failures of digestion, assimilation, nutrition and elimination, hardening of tissues and loss of function.

All the reactions of digestion, assimilation and elimination are colloidal. All the reactions of the ferments and enzymes are colloidal. The reactions of ferments and enzymes are peculiar, in that they are intermediate in organic chemistry, and accomplish a compelte chemical process, end reaction or end product without the violence of an immediate chemical reaction. The enzyme or intermediary is then set free to enter again upon its reaction cycle, and theoretically is not lost and should be able to act to infinity. Some of the minerals in their colloidal combinations have the power to act as enzymes. This is especially true in the toxicology of pellagra.

The two colloids coming from clay and of interest in the etiology of pellagra are hydrated silica or silicic acid (SiO_2) and hydrated alumina (Al_2O_3). From the analyses given in different parts of this work it will be seen that in all ordinary clays, as in the rocks from which the clays are derived, the silica greatly predominates. In colloidal sols or conditions of great dispersion, as clay is always found in drinking water, these two colloids are incompatible, electrolytic, and mutually precipitate each other. Since the silica is so greatly in excess, the alumina is all precipitated and only the excess of silica remains to be a toxic factor in the etiology of pellagra. If it were possible to have a general excess of alumina, as actually occurs in limited deposits of bauxite ores, the toxicology of alumina instead of silica would present itself.

The toxicology of silica is in close relation with the turbidity of potable water. Turbidity in potable water may be defined as the inhibition of light by material in suspension. Water sanitarians are generally agreed that the esthetic objections to a turbid water are of such a degree that nobody will use a water as a common beverage when the turbidity attains one hundred parts per million. A turbidity of 5 or 6 jarts per million is the standard of clear potable water. The turbidity of colloidal silica is a slight opalescence, and even at ten parts per million, the dilution or colloidal dispersion is very great. This turbidity, or even somewhat greater, is commonly found in streams coming from clay soils and in springs and wells in clay regions and having clay bottoms which are readily stirred up on drawing water.

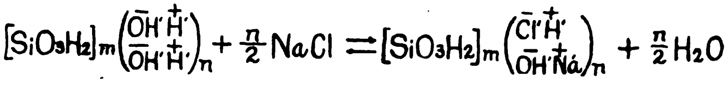
Colloidal silica is readily absorbed by both the animal and vegetable organism. If absorbed or administered hypodermically in considerable amount to the laboratory animals it kills in from 30 to 60 days. Ingested in drinking water its toxic course is generally chronic, being modified by the amount of silica in the water, the antidotes in the water and food, the amount of water taken, the susceptibility, resistance and elimination of the patient. Taken in great amount by plants, it stunts growth, dehydrates and hastens ripening.

Colloidal silica acts like an enzyme. The toxic effects are secondary and not direct. The silica acts as a colloidal intermediary, fixing the bases of the mineral salts in the protoplasm of the tissue cells, substituting water and setting free the acid of the salt. The silica is again set free and theoretically would act to infinity unless eliminated or rendered innocuous. Thus by a slow colloidal reaction, silica fixes the sodium, potassium, magnesium and calcium of the chlorids and sets hydrochloric acid free. It fixes the same minerals of the phosfates and sulfates and sets free phosforic and sulfuric acid. With each reaction a portion of water is also removed from the tissues. As the chlorids make up such a large part of the solids or salts, hydrochloric acid intoxication is one of the salient features of pellagra. Water exhaustion is the other important manifestation. It is suggested that silica also fixes the salts of the carbonates and that carbon dioxid is very mild and readily eliminated, it plays no part in the intoxication. In fact, for this reason the carbonates are the most important antidotes to silica intoxication.

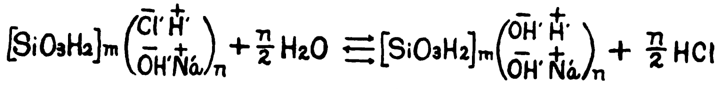
For the reasons just stated, if a water containing silica in colloidal solution or suspension be ingested, the ingestion of chlorids, sulfates or phosfates only intensifies the intoxication as it furnishes the salts to be dissociated, setting the acids free to increase the acid intoxication. So in the prophylaxis of pellagra by drinking "hard" water, it must be understood that the hardness of the water must consist in the "temporary" hardness of the carbonates of calcium and magnesium, and not the permanent hardness of calcium chlorid and calcium sulfate.

Colloids in suspension in water are sometimes said to be in a flocculent state. Reagents which tend to concentrate and precipitate such colloids are said to deflocculate the colloid. This is accomplished by electrolytes which concentrate, coagulate or precipitate the colloid, at the same time extruding water and freeing acid to a colloidal equilibrium. The electrolytes commonly occurring in nature or readily applicable to drinking water are the chlorids, sulfates, phosfates and carbonates of the alkalies and of the alkaline earths. As already indicated, the chlorids, sulfates and phosfates can only contribute to an increase and aggravation of the acid intoxication. The opposite is true of the carbonates. The carbonates are equally powerful to engage the attention of the silica in its round of enzymatic action. A small amount can act as an electrolyte for a large amount of silica. But this action has no injurious effect, because the acid set free is CO_2 instead of HCl or H_2SO_4, as in the case of the chlorids and sulfates. The carbon dioxid is readily eliminated by the respiration and no intoxication results. Since electrolytic action proceeds in direct relation to valence, the carbonates of magnesium and calcium should have a greater antidoting power than the carbonates of sodium and potassium.

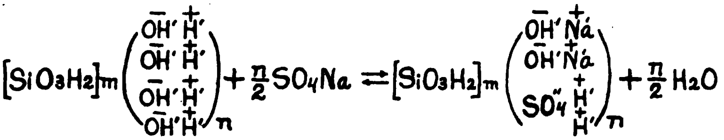
The various reactions suggested above may be illustrated by the following formulae:



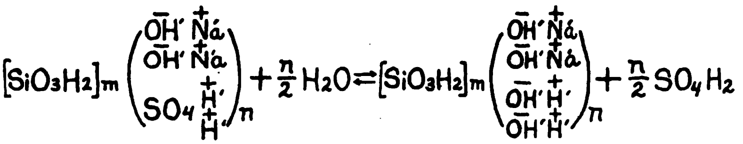
$$[SiO_3H_2]_m\begin{pmatrix}\overset{-}{OH}'\,\overset{+}{H}'\\ \overset{-}{OH}'\,\overset{+}{H}'\end{pmatrix}_n+\frac{n}{2}NaCl\rightleftharpoons[SiO_3H_2]_m\begin{pmatrix}\overset{-}{Cl}'\,\overset{+}{H}'\\ \overset{-}{OH}'\,\overset{+}{Na}'\end{pmatrix}_n+\frac{n}{2}H_2O$$



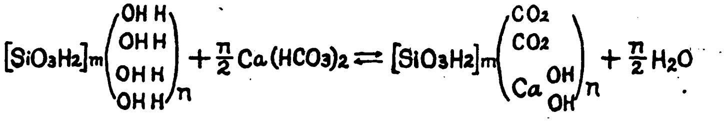
$$[SiO_3H_2]_m\begin{pmatrix}\overset{-}{Cl}'\,\overset{+}{H}'\\ \overset{-}{OH}'\,\overset{+}{Na}'\end{pmatrix}_n+\frac{n}{2}H_2O\rightleftharpoons[SiO_3H_2]_m\begin{pmatrix}\overset{-}{OH}'\,\overset{+}{H}'\\ \overset{-}{OH}'\,\overset{+}{Na}'\end{pmatrix}_n+\frac{n}{2}HCl$$



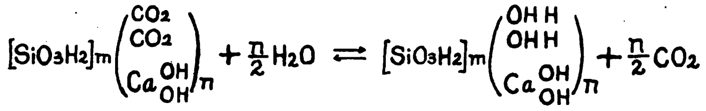
$$[SiO_3H_2]_m\begin{pmatrix}\overset{-}{OH}'\overset{+}{H}'\\ \overset{-}{OH}'\overset{+}{H}'\\ \overset{-}{OH}'\overset{+}{H}'\\ \overset{-}{OH}'\overset{+}{H}'\end{pmatrix}_n+\frac{n}{2}SO_4Na\rightleftharpoons[SiO_3H_2]_m\begin{pmatrix}\overset{-}{OH}'\overset{+}{Na}\\ \overset{-}{OH}'\overset{+}{Na}\\ SO_4''\,\overset{+}{H}'\\ \overset{+}{H}'\end{pmatrix}_n+\frac{n}{2}H_2O$$



$$[SiO_3H_2]_m\begin{pmatrix}\overset{-}{OH}'\overset{+}{Na}\\ \overset{-}{OH}'\overset{+}{Na}\\ SO_4\,\overset{+}{H}'\\ \overset{+}{H}'\end{pmatrix}_n+\frac{n}{2}H_2O\rightleftharpoons[SiO_3H_2]_m\begin{pmatrix}\overset{-}{OH}'\overset{+}{Na}\\ \overset{-}{OH}'\overset{+}{Na}\\ \overset{-}{OH}'\overset{+}{H}'\\ \overset{-}{OH}'\overset{+}{H}'\end{pmatrix}_n+\frac{n}{2}SO_4H_2$$



$$[SiO_3H_2]_m\begin{pmatrix}OH\,H\\ OH\,H\\ OH\,H\\ OH\,H\end{pmatrix}_n+\frac{n}{2}Ca(HCO_3)_2\rightleftharpoons[SiO_3H_2]_m\begin{pmatrix}CO_2\\ CO_2\\ Ca{}^{OH}_{OH}\end{pmatrix}_n+\frac{n}{2}H_2O$$



$$[SiO_3H_2]_m\begin{pmatrix}CO_2\\ CO_2\\ Ca{}^{OH}_{OH}\end{pmatrix}_n+\frac{n}{2}H_2O\rightleftharpoons[SiO_3H_2]_m\begin{pmatrix}OH\,H\\ OH\,H\\ Ca{}^{OH}_{OH}\end{pmatrix}_n+\frac{n}{2}CO_2$$

A study of these formulae shows that the end product of the double reactions in the first two sets of formulae is a noxious and toxic acid, and that the end product of the last set of formulae is a harmless product easily eliminated. This is the real reason why pellagra is not found in limestone countries where the water has a temporary hardness derived from the carbonates of lime and magnesia, and why pellagra may be worse in a silicious region high in chlorids and sufates. These principles will be applied in the discussion of the prevention and treatment of pellagra. It will be noted further that the first of each series of combinations results in a loss of water from the colloid. This results in the drying which is so prominent in the pathogenesis of pellagra.

CHAPTER VIII.

THEORIES AS TO THE CAUSE OF PELLAGRA.

The cause of pellagra has long been a subject of controversy. The reasons for the difference of opinion lie in the methods of research. For many years it has been the custom in the investigation of diseases of unknown origin, to formulate a hypothesis of the origin or etiology of a given disease to be investigated. In this way many able investigators have become partisans of their hypotheses, and instead of a true investigation of the diseases from the bedside study of the clinically obvious, they have sought data to establish their hypotheses. Pellagra is one of the most conspicuous examples of this condition of research. Even now, after the cause, prevention and treatment of pellagra have been scientifically established, the rivalry between the advocates of disproven hypotheses is as keen as ever.

The most prominent theory of the cause of pellagra is the eating of corn meal. Some have insisted that corn was an unbalanced diet and that toxic conditions were created thereby. Others have insisted that the cause was spoiled corn meal. More work has been done, more effort spent to prove that pellagra is caused by spoiled corn, than has been spent on any other theory. This theory seems to have arisen soon after the discovery of the disease. It seems to have been held for some time and was formulated about 1810 by Marzari. Marzari thought that corn was deficient in certain nutritive principles. Balardini insisted that the disease was due not to good corn, but to moldy corn, and accused a certain green mold sometimes found on corn. Lombroso took up this theory and is largely responsible for its wide acceptance.

However, the strongest advocates of the corn or maize theories have always fallen short of actually proving any direct relation between the maize (Italian granoturco) diet and pellagra. Others have strenuously insisted that there are regions where pellagra is found where maize is not eaten, and that there are other regions where maize is the principal cereal diet and where pellagra does not exist. We might indulge in an extensive discussion of the elaboration of this theory, especially by Lombroso, but as the theory failed of establishment, it is now only of historic interest in a discussion of pellagra.

Another prominent theory is that pellagra is a parasitic disease carried or transmitted by some blood sucking insect. This theory dates from 1905, is about ten years old, and was first announced by Sambon. Sambon has not fixed upon the parasite; this is still hypothetical. But he has decided that the carrier is some species of the simulium fly or so-called "buffalo gnat." Sambon has tried to build up a series of facts to support his hypothesis. He insists upon the agreement of pellagra with certain phenomena of other parasitic diseases, that the geographical distribution of pellagra agrees with the geographical distribution of the simulium fly and that the seasonal incidence of the cutaneous manifestations of pellagra coincides with the active life cycle of the fly. While Sambon is still in the active advocacy of this theory, it must go the way of all hypotheses not founded on fact.

In 1910, Alessandrini of the Institute of Experimental Hygiene of the University of Rome, suggested that pellagra might be caused by certain filaridae, a species of nematode worm. He only published a preliminary note. Further investigation convinced him of his mistake, and about two years afterward in collaboration with Scala of the same Institute, he announced the true cause of pellagra.

In 1909 and 1910, Siler and Nichols, Long and Young suggested that pellagra was a form of amebiasis. Pellagra is prevalent in countries where the intestinal tract is often infested with ameba. The intestinal disturbances of pellagra suggested an analogy.

Another theory is that the use of cottonseed oil instead of lard may be a cause.

The latest theory, and one equally untenable with all the others, is the lack of proteids in the diet. It is stated that pellagra is a disease of the poor and poorly nourished. That in a well balanced and nutritious diet lies the prevention of pellagra. However, all of these theories fall before the true cause of pellagra.

The Modern Research Phase.

In research work in the cause of human disease, it is very desirable to be able to refer to the work of others so that established truth may be ascertained, and that no time be lost in doing over what has already been well done. In this regard, we desire to note and follow what has been established along the lines of rational research in pellagra in this country.

For some time Spartanburg County, South Carolina, has been a favorite field of research in the etiology of pellagra. Over ten years ago the Bureau of Soils of the United States Department of Agriculture made a very careful survey of the soils of this county in connection with an area immediately to the west. The area was surveyed and mapped on such a large scale that the map of a comparatively small area is as large as a common table top. The description of the soils of this area, called the Campobella Area, from a small town in the area, constitutes a monograph which is the most complete account we have been able to find of the general prevalence of pellagra in Spartanburg County, South Carolina. The title of this monograph is "Soil Survey of the Campobella Area, South Carolina," Bureau of Soils, Washington, D. C.

This monograph shows that all the soils of this county are clay, that the drinking water supply must come from these clays, that this water must necessarily carry silica in solution and be pellagrogenic.

Similar soils surveys have been made of almost all the pellagrous area. These are published with elegant maps by the Bureau of Soils and are available for free distribution to any student of pellagra. A vast amount of this modern research has been done. There only remains the prevention and treatment of pellagra.

Pellagra is a common disease of the domestic animals of pellagrous areas. They drink the same water and are subject to the same toxic action of the silica contained therein. Giovanni Marchese in his Dizionario di Agricoltura, Vol. V, page 118, published in 1898, makes the following statements concerning pellagra in domestic animals. We translate from the Italian:

"It is manifest (pellagra) in diverse forms and with a variable course, has an evolution either acute or excessively mild, with phenomena less numerous or multiple, evident or entirely rudimentary. It is considered as an affection belonging to the human species, but now it rages among the bovine animals and also with less frequency among the other domestic species. In the bovine animals pellagra has an evolution mild and obscure; it changes, with time, to a progressive emaciation without obstructing greatly the different functions of the economy. In general, the authorities recognize in this disease three periods quite distinct: a failure of appetite which is manifest at intervals, a certain disgust of liquid food, a diminution of the rotundity of form, dirt eating, a perversion of taste, which prompts the animal to ingest substances extraneous to alimentation, disturbances of the respiration, dryness of the skin which seems adherent to the tissues beneath, a strong disagreeable odor which develops from the whole surface of the body. Such are the principal manifestations of the first period."

"The second period is characterized by the following symptoms: The skin is wrinkled and hairless in spots; the depravation of taste is more pronounced; the buccal mucosa is dry, wrinkled, inflamed; the leanness always becomes worse, the expression shows hebetude; the eyes are sunken in the orbit; the look is without expression. Soon locomotion becomes difficult; intermittent febrile attacks, chills and tremors are manifest."

"In the third period, especially the nervous phenomena occur. The febrile attacks are frequent and the animals rush against resisting bodies (manger, columns, walls) which are excitants to them; they paw the ground; they open the mouth; they try to bite and make a sound of plaintive bellowing. They finally die in one of these attacks. During this last period an abundant diarrhoea appears, entirely liquid and extremely fetid."

In 1914, Alessandrini and Scala quote Marchese with approval and state further that there is:

"Especially among the cattle, a disease commonly called *tignuola,* which is manifest in the spring with a depilation in spots on the sides of the neck, the breast, and in cases more grave, also on the back, with decrease of strength and general decline. All these phenomena disappear with the coming of winter but are manifest again in the coming spring."

"Only those animals are subject to this disease which live in the country where it extends to the dogs and also to the cats living with pellagrous families."

Although the toxicology of silica had been worked out and published seventy-five years ago or more, and pellagra was confined to those regions of the earth where the water supply was derived from clay soils, and the symptomatology of pellagra and chronic intoxication with silica are identical, all these facts, together with those given immediately above, seem to have been overlooked.

It remained for Professors Giulio Alessandrini and Alberto Scala of the Institute of Experimental Hygiene of the University of Rome to break away from the old methods of research, to adopt the method of research in the clinically obvious in the study of pellagra, and announce the true cause, prevention and treatment of the disease.

They published their preliminary note on May 25, 1913. It bears date of May 22nd. Professor Alessandrini sent the writer a copy. He translated it into English and published it. Alessandrini and Scala published their complete monograph early in 1914, and sent the writer two copies with the request that he translate and publish it in English. For this purpose they sent the original half-tone plates which illustrate the original work. This translation is Part I of this work.

THE CAUSE OF PELLAGRA.

According to Alessandrini and Scala the following are the facts as to the etiology of pellagra.

Pellagra is a chronic acid intoxication caused by colloidal silica in the water supply.

Pellagra is strictly localized and contracted in those regions where the water supply is derived from clay soils.

It is the silica in suspension or in colloidal solution in these water supplies, taken daily with the drinking water in very small amounts by the people drinking such a water for many years which is the cause of this dreadful disease. It is no fault of the people; it is not because they are unsanitary, or poor, or hard at work, or live in luxury. It has no relation to flies or gnats or mosquitoes; nor to corn meal, or cotton seed oil or diet. It is not a matter of abstruse research, or bacteriology, or serums, or toxins or antitoxins. It is just a simple matter of drinking "soft" or "freestone" water in a clay country.

Because pellagra is due to clay in drinking water, we have devoted considerable space to a discussion of clay in the soils of the southern states. In discussing clay we were discussing the cause of pellagra. The essential noxious constituent being colloidal silica, and colloidal silica taken in small quantities over a long period producing a chronic intoxication, we will devote some space to the toxicology of silica.

CHAPTER IX.

TOXICOLOGY OF SILICA.

In this connection the toxicology of silica is a very important question. It seems that many investigators have considered silica inert. Since quartz is silica, all silica was looked upon as being as insoluble as quartz. But some other forms of silica are soluble. They are also readily absorbed into the animal organism and exert profound changes in the tissue cells. I find that this character of silica has not been overlooked by all scientists. The toxicology of silica has been well known for at least seventy-five years. The writer has access to half a dozen volumes and many journals in a medical library of a few thousand volumes, which give the toxicology of silica in full. Samuel Hahnemann in Germany had worked out the toxicology of silica and published his results by 1830. He was followed by many others in this investigation. His work was translated into French and published in Paris in 1846. Many large works in German soon followed the work of Hahnemann. Others in England and America added largely to the investigation of silica.

The toxicology of silica as evidenced in pellagra is necessarily of the chronic form. The silica taken in water is very dilute. It requires years to make its victims sick. This chronic intoxication of silica may be briefly stated as follows:

Brain and nervous system:

Indifferent, confused, compunction of conscience, overanxious, low spirited, gloomy, sensitive to noise, weeps.

Vertigo, inclined to fall forward, sense of things whirling around.

Headache, gray veil before the eyes, sense of pressure in the head.

Sense of weakness, inability to lift any weight, sense of constriction of the chest; palpitation of the heart; heart trouble from nervous exhaustion; rapid pulse; circulation easily agitated.

Weakness of back and lower limbs, incoordination of gait followed by paralysis of lower limbs; tremors.

Tremors of upper limbs, shaking of hands, arms feel heavy, numb, as if needles were stuck in them; paralysis of hands; drawing up of fingers, clenching; spasm of hands.

Trembling and sense of weakness in limbs in general; limbs sore, as if going to sleep, stinging pains and sensations. Drowsiness, lassitude, depression, restless sleep, frequent waking, starting with trembling of whole body.

Sensitive to change of temperature; susceptible to stimuli.

Tissues:

Emaciation with pale suffering expression; tissues dry; peritoneal, pericardial and pleural fluid scant or wanting; serous membranes dry; muscles dry, pallid, stuck together.

Skin:

Skin dry, wrinkled and folded; not attached to subcutaneous tissues; desquamation, falling of hair; erythema and pigmentation, especially on exposed surfaces, worse in warm weather or on the application of artificial heat.

Digestive System:

Perverted taste, tongue sore, fissured, red, purplish, water tastes bad, vomits after drinking.

Acidity of mouth, dryness of mouth, silivation, pyrosis.

Throat dry, sore, burning.

Canine hunger with disgust for food; thirst.

Sour eructations after eating, heartburn, sense of weight in stomach, pyrosis. Nausea and vomiting. Hiccough, belching, stomach sensitive to pressure, gastralgia.

Burning from mouth to anus; thickening and induration of the pylorus, thinning of the walls of stomach and intestine, atrophy of intestinal musculature.

Constipation, very hard stool, covered with mucus, burning at anus, difficult to pass stool; great straining.

Frequent scanty, liquid, offensive diarrhoea; watery, weakening, frothy, mucous or bloody, putrid.

Mucous Membranes:

Red, purplish, inflamed, very sore; tongue furrowed; denuded of epithelium; lips denuded; digestive tract ulcerated.

Vulva and vagina red, inflamed, very sore.

Urinary organs:

Urine scant, low in mineral solids; paralysis of the baldder and spasm of sphincter, retention of urine; enormous distension of bladder.

Paralysis of the sphincter, incontinence of urine; constant desire to urinate.

The Pathogenesis of Silica.

When colloidal silica is taken into the human system in drinking water it is absorbed and enters into combination with the proteid substance of the tissue cells. However, it does not stop here. It acts much like an enzyme; that is, the combination is only a step in the process of uniting or fixing salts in the tissue cells. When the tissue cells have combined with the silica they are then in a condition to make a new combination with the salts and alkalies. This combination is made, the salts fixed in the cells and the silica again set free.

The silica again goes through the cycle of attaching to proteid substances and fixing salts in the cells. So with the continued ingestion of silica and the setting free of the silica already in the body to go through the cycle again, it can readily be seen that the action of silica is cumulative.

Now every time that silica is able to attach a salt to a cell or to protoplasmic substance it frees water and the acid which formed the salt. Since hydrochloric acid is the most common acid in the combinations of the salts of the body, it is the acid most commonly set free by the action of the silica.

The abstraction of water results in the drying of the tissues so marked in pellagra. The freeing of the acids is the cause of the acid taste, the burning, and the skin manifestations of the disease called pellagra.

The fixing of the salts in the tissues causes them to be very low in the urine, until there is an accumulation in the tissues so great that it can no longer be tolerated. Then for a time there is a larger excretion of chlorids and phosfates in the urine. When the great excess has been eliminated, there is a return to the accumulation above the normal.

The normal condition of the human body is an alkalinity of 0.85% when measured by a solution of sodium chlorid. When this alkalinity is decreased by the liberation of an excess of acid, there is a tendency to ulceration. This is the condition of the whole intestinal tract in pellagra.

The withdrawal of water has a marked effect on the nervous system. As in all drying processes, there is first excitement and hyperesthesia, followed as the drying progresses, by incoordination and paralysis. The same thing takes place in alcohol intoxication.

CHAPTER X.

THE SYMPTOMATOLOGY OF PELLAGRA.

The symptoms of pellagra are divided into three general classes:

1. The cutaneous manifestations.
2. The digestive disturbances.
3. The nervous disturbances.

These are called the classical triad of pellagra.

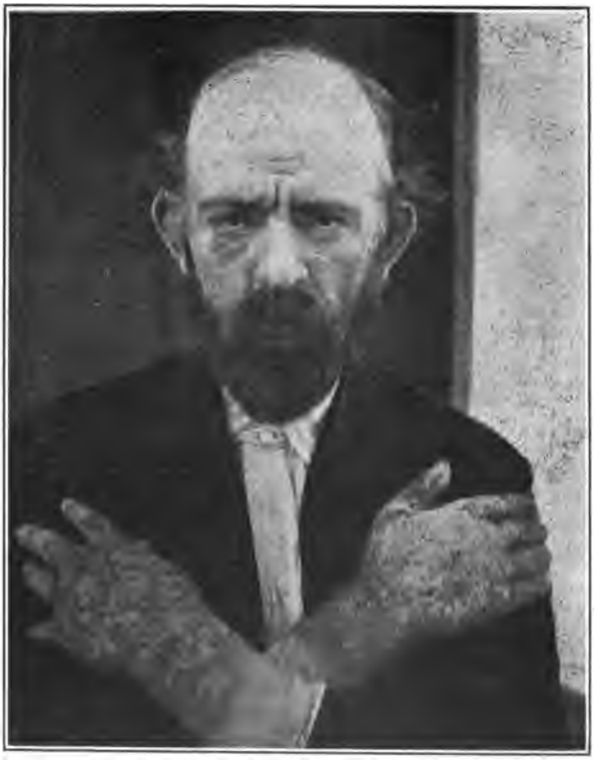
The digestive disturbances are evidenced by a loss of appetite, a perverted taste, a disgust for food, bad tastes in the mouth, soreness of the mouth, lips and tongue, burning of the throat, burning in the stomach, belching, sour eructations, hiccough, nausea and vomiting, indigestion with attendant weakness and emaciation.

There is at first generally a severe constipation, with loss of vigor and tone of the intestine, inability to pass stool due to hardness of stool, lack of lubrication, and weakness of the intestinal muscles. Stools hard, dry, covered with mucus and sometimes streaked with blood. Often no operation of the bowels for days or a week. Requires some time with an enema to clean out the bowels.

The constipation may be followed or alternated with a diarrhoea. This is generally scant, frequent, liquid, frothy, weakening and very offensive.

The nervous disturbances are generally those of excitement in the earlier stages of the nervous manifestations, followed by depression and paralysis.

The patient is easily excited, intolerant of noise, starts up readily, is generally hyperesthetic. Easily aroused from sleep, starts at the least sound.



Pellagra—From Tranasctions of National Conference on Pellagra, 1909.

This stage is followed by a period of apathy, discouragement, loss of ambition and initiative. The patient does not want to do anything, work is difficult, has vertigo, feels in danger of falling forward, everything seems to spin around, there is a loss of confidence, self-consciousness, religious emotions, the patient loses hope, thinks he will die, has no faith in treatment, and even discounts his own improvement under treatment.

There is loss of strength, especially in the lower limbs, and inability to lift weights. The legs tremble and give way at the knees. There is incoordination of gait, a dragging of the feet and finally paralysis of the lower limbs.

There is tremor of the hands, an inclination to spasm of the hands with clenching of the fingers. Finally paralysis of the upper limbs.

The mental symptoms may grow worse to melancholy and insanity of the peculiar pellagrous type.

The cutaneous manifestations or pellagroderma are generally worse at the change of seasons, especially at the advent of warm weather in the spring. They depend upon the amount or degree of the acid intoxication, and their seasonal manifestation is due not to sunlight but to sun heat. They may be brought on by artificial heat such as work in the kitchen or over the wash tub. Because of the concentration of the acid poison in the system by evaporation, the cutaneous manifestations appear first on the exposed parts of the body, and present the classical gauntlet and mask, that is, they appear below the wrist band and above the collar.

These manifestations are of two kinds; pigmentation and erythema or reddening of the skin. Some persons scarcely have the reddening, blistering and scaling of the skin. They just turn brown over the exposed areas, and this browning is very different from tan. It is a true pigmentation. In addition the skin becomes tender and may scale off.

In other instances the skin scales, scabs, becomes sore and ulcerates. Under the scaling surface the skin is very red. The hair comes out in spots. The sores run together and become quite extensive. The skin is very dry, is wrinkled and folded and seems to be free from the underlying tissues. It has the same burning sensations mentioned in the digestive tract, due to the acid condition of the system.

After the advent of warm weather, when the patient has eliminated much of the acid poison by sweating, the skin lesions generally improve, but may be worse again for a time on the recurrence of cold weather when elimination is checked.

Persons who are full of the acid intoxication have the skin lesions early in the spring as soon as there is some warm weather; those having less of the intoxication, present the skin lesions later in the season. However, these lesions are due to heat and not to light. They may be brought on in the kitchen or over the wash tub just as readily as out in the sunshine.

The foregoing symptomatology is the personal observation of the writer. An extensive reading of the subject discloses many excellent statements of the symptoms of pellagra. One of the best in our opinion is given by Dr. George F. Gaumer, of Izamal, Yucatan, Mexico. From his description we quote in part:

"Prodromes—Lassitude, ocular phenomena, vertigo, headache, general weakness and occasional digestive disturbances."

First Stage.

"Symptoms.—A patient upon first consulting a physician complains of a sensation of heat in the mouth, throat and stomach, upon the exhalation of the breath; taste is impaired, there is anorexia and frequently ptyalism with a broad, flabby tongue irregularly marked by red blotches, a peculiar formication in the extremities which often extends very gradually to the whole of the body. About this time small, smooth and very lustrous specks make their appearance on the dorsal aspects of the hands and feet. These specks, when first noticed by the patient, are no longer than a pin head, but rapidly become more numerous until uniting they form lustrous patches which are checkered off in little squares, and these are separated by fine lines, thus giving the cutis a scaly appearance, which is better seen by drawing the skin together with thumb and finger. This often covers the whole of the body, but is generally confined to the extremities, chest and back. The skin takes on a senile appearance and the itching becomes almost intolerable, and if scratching be resorted to for relief the burning that follows is unendurable."

"About this time the strength begins to fail, and the patient walks with a heaviness and a peculiarity in his step that he does not understand. He can no longer find his way with closed eyes. The reflexes become greatly exaggerated and his movements are incoordinate. His sleep is much disturbed by hallucinations and strange dreams. During his waking hours he examines himself minutely and with frequency, and soon begins to carry on a constant, though inaudible, conversation with himself or some imaginary companion."

"In conversation with other persons it soon becomes evident that the mind wanders. Before completing one subject another is begun. Meaningless words are thrown in and as important ones left out. The patient's description of his disease becomes long and tedious, and he often ascribes as a cause of his present condition some insignificant disease or injury that befell him in his youth."

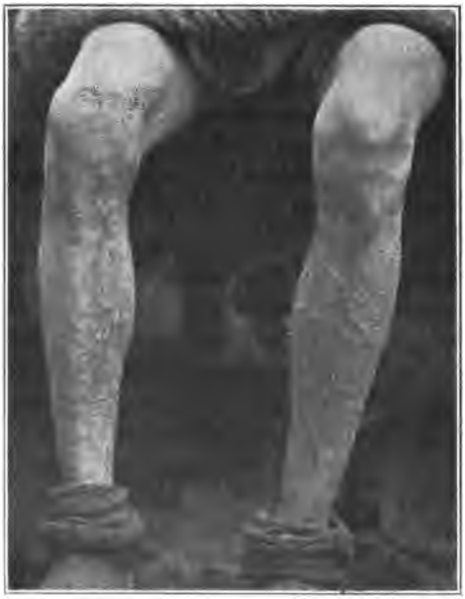
Second Stage.

"As time goes on the physical sufferings become greater and greater, the skin wrinkles more, the appetite fails and this is due to the perversion of the special senses of taste and smell, so that the patient looks upon the most savory dishes, all kinds of drinks and even his medicines as filthy substances calculated to aggravate his sufferings if not to kill him. Hunger increases the mental derangements. Strength fails until the patient is confined to his chair or bed. The mind becomes more deranged as the itching and burning continue to reach his nervous system, so that he often seeks to put an end to his sufferings by committing suicide."

"The bowels at first were often constipated, but as the disease advances a diarrhoea sets in, which is accompanied by a progressive emaciation, until the patient is reduced to a mere skeleton, or, in some cases, it passes into a dysentery, which, running a rapid course, soon terminates fatally."

Third Stage.

"Inasmuch as pellagra is a disease in which every symptom from its first appearance advances progressively to a fatal termination the third stage is but the first and second in a state of progression in which the mental and physical phenomena predominate. Fear of impending danger often makes the patient want to flee from home and friends, and to take refuge in the forest, but, upon finding himself devoid of strength and the power of locomotion, his fright increases, and he strives to escape from an imaginary bondage. Friends are no longer trusted, but are treated as enemies."



Case of Drs. Gates & Gates, Waco, Texas.

"All former symptoms are progressively intensified until the patient loses control of the mind and complete dementia generally occurs near the termination of the disease."

"All psychoses are of the melancholic type and tend to make the patient cowardly, rarely becoming aggressive."

"Weeks, months and sometimes years are spent in this stage, during which time the patient gradually grows weaker until he is unable to swallow food or drink, to utter an audible word or to voluntarily move a single muscle; thus the spark of life is slowly but surely extinguished."

"In Yucatan pellagra is not influenced by seasons." Ulcers and ulcerative processes from no part of pellagra, but when they do occur as complications they are very obstinate and difficult to cure."

Pellagra.

1. "In the beginning of the disease patient complains of a sensation of heat in the mouth, throat and stomach on expiration."

2. "Sense of taste impaired; there is anorexia and ptyalism."

3. "Tongue broad, flabby and irregularly marked by red blotches."

4. "Bowels constipated, followed by diarrhoea and sometimes dysentery."

5. "Cuticle assumes a scaly appearance; scales lustrous, thin and not detachable until disease is far advanced—seldom pigmented; only affects the cuticle."

6. "Pruritis and burning deep-seated, aggravated by scratching. Affected differently by sun and shade."

7. "Muscular weakness marked and progressive."

8. "Vertigo, occipital headache, insomnia, neuralgias and cramps."

9. "Ocular phenomena generally present."

10. The gait is usually paralytic, occasionally paralytic spastic and progressively ataxic."

11. "Mental phenomena progressive from slightest perturbation to complete dementia."

12. "The pellagrin avoids company, seeks solitude, is distrustful, melancholic, avoids conversation, prefers the dark, wants no assistance."

13. "Epileptiform movements rythmic and often continued to death."

14. "Pellagra is not limited to season, age, sex nor condition in life."

15. "The pellagrin does not fear death, generally unconscious at death."

In a Bulletin on Pellagra issued by the Louisiana State Board of Health, the following statements are made concerning the symptoms of pellagra:

Symptoms of the Digestive Tract.

"Stomatitis, esophageal burning, pyrosis, gastralgia, belching, nausea, gastritis, dyspepsia, diarrhoea usually, and constipation rarely."

Cutaneous Symptoms.

"Limited to parts of the body which are exposed to direct rays of the sun. On the hands, eruption appears on the backs. Knees may show eruption as well as backs of elbows. In every instance the disease is symmetrical. It is sharply limited to the area exposed to the sun, and there is no gradual passing of diseased to healthy skin. The color of the eruption differs according to the period at which it is seen and the color of the individual. It is rare, however, that the color is similar to that seen in sunburn. The color becomes deeper as the eruption becomes older, and then it does not disappear under pressure, and may attain a reddish brown or a tinge of sepia. The first eruption may disappear in a short time, two or three weeks. The skin peels off in light flakes and leaves a pigmentation varying with the severity of the preceding conditions. The skin is tense and swollen, and burning may be complained of. It rarely itches, and the surface is not commonly scratched."

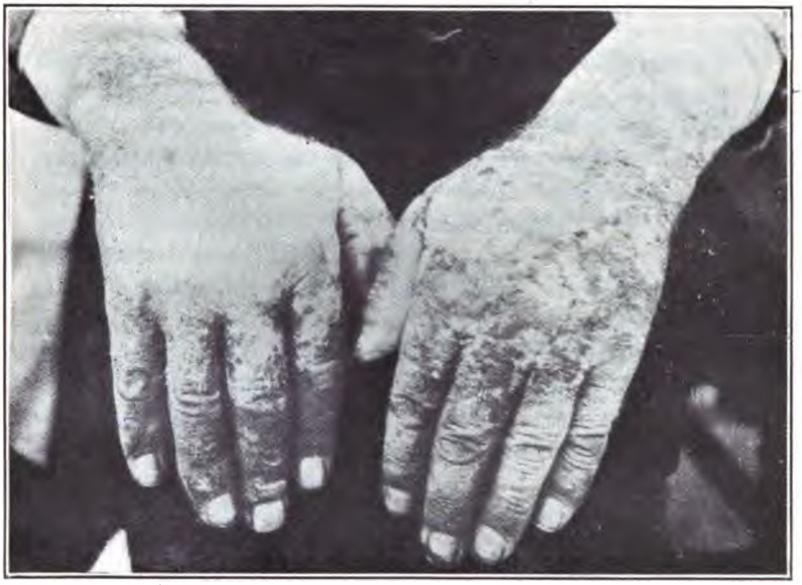
The Chief Nervous Symptoms.

"Chronic neurasthenia, vertigo, headache, tremor, sensation of fatigue and backache, ataxia, spastic and paralytic gaits, paralysis and paralytic strokes."

Mental Symptoms.

"Sadness, melancholia, dementia, mania, confusional insanity, mutism, murder and suicide."

"It has been frequently observed that the skin lesions of pellagra, although having given the disease its name, are by no means necessarily, or even commonly, the first symptoms to appear. It is perhaps less generally known that symptoms referable to other organs may persist for such a long period without the development of the dermatitis that one may be entirely put off the scent if one depends on this symptom alone."



Pellagroderma of Hands—From Transactions of National Conference on Pellagra, 1909.

"A very red, fiery and painfully burning tongue is quite characteristic. The sensation of burning is felt all down the throat and gullet to the stomach. Diarrhoea is generally present. It may alternate with constipation. The stools are very offensive. In my experience, these digestive symptoms from mouth to intestines are the most uniformly present and most characteristic."

"The skin symptoms consist of a bright red sunburn with thickening, roughening, scaling of the skin. As the skin scales off it leaves behind a pigmentation similar in appearance to that of sunburn, and also similar in its distribution—the hands and forearms, the face, neck and upper chest.

The line between the affected and unaffected skin is sharp as is sunburn. When one passes his fingers over the affected skin it feels as if sand were in the skin."

"The nervous symptoms from nervousness through melancholy to insanity are usually later and of less diagnostic value than the digestive disturbances and skin changes."

"Pellagra, unlike a garment, is not made to pattern, and these symptoms are subject to great variation. These manifold symptoms vary in their order, in number, in association, and in severity. The first symptom may be the dermatitis, and for the first few seasons it may be the only noticeable symptom. There may be a dermatitis and malaise, with entire absence of gastro-intestinal symptoms. The skin may itch and burning sensations be absent. The attack may be so slight that it interferes with neither work, sleep nor strength; or so severe that the first attack is malignant pellagra and death comes quickly. The dermatitis, instead of dry, may be of exudative type, with vesicles, rupture and ulceration. Constipation may occur and diarrhoea be absent even in the period of outbreak. The neurasthenic element may be absent, weight may remain as usual, and good spirits, instead of depression, be the rule. Appetite may continue as usual, or even be increased to greediness. Thirst may increase, or there may be a repugnance to water. Lassitude, dermatitis and a tongue without a coat are the rule."

Resistance and Predisposition.

All the principles of natural resistance and predisposition apply in the matter of contracting such a disease as pellagra or in being immune therefrom. In persons of vigorous constitution who eliminate readily, the intoxication may never have serious manifestations. It is well known that many persons of peculiar physiology absorb readily and do not eliminate at all. Such persons are generally the victims of the chronic intoxications. If such a man is a painter or works in a lead mine or at a lead smelting furnace or in a type foundry or is a plumber, he will have lead poisoning. If for any reason he is below par, or works too hard, or has some undue exposure, or has trouble or is much worried, so as to reduce the vital force, he will suffer from the intoxication. The same is true of the intoxication from silica. People of less active physiology, diminished resistance, those who are worried and troubled so that the processes of nutrition and elimination are deranged, are liable to the intoxication if they drink a soft water high in silica. So in answer to the question or criticism as to why only a few persons in a pellagrous area contract the disease, it is proper to say that the same factors of immunity and individual resistance, individual weaknesses, failure of elimination of poisons and individual susceptibility, apply in the case of pellagra just as they apply in the contraction of or immunity to any other disease.

Pellagra is essentially a disease of a fixed agricultural population, living on a soil of determinate geological origin, which has been denuded and cultivated long enough to have lost its original alkalies. The water supply commonly drunk must be derived from this soil. This water must be drunk long enough for the accumulation of silica to produce the symptoms of the intoxication.

In new countries the soil that has been covered with timber and has not been washed, leached and gullied, has its original alkalies. Prairie lands are alkaline or they would not be prairie. Even the much smaller amount of alkalies of new timber lands are a protection against pellagra for a few years.

Persons who move from place to place and change from a pellagrous or freestone water to a limestone water do not exhibit the symptoms of pellagra because the limestone water soon neutralizes the action of any silica which may have been absorbed.

CHAPTER XI.

THE PREVENTION OF PELLAGRA.

Since pellagra is a chronic acidosis caused by the ingestion of colloidal silica, its prevention consists in providing a drinking water of the proper alkalinity. It is well known that silica is antidoted and rendered perfectly harmless and inert by the alkalies and the alkaline earths as they are found in nature, that is by the alkaline carbonates and the carbonates of the alkaline earths. The alkaline carbonates are the carbonates of sodium and potassium. The carbonates of the alkaline earths are the carbonates of calcium and magnesium. The most common form of the carbonate of calcium is common limestone. When limestone is in solution in water it makes the water hard. This is what is called "temporary hardness," which is precipitated by boiling and makes "scale" on the inside of cooking vessels. People who drink this hard water do not have pellagra. So the simplest thing to do in order to avoid having pellagra is to drink hard or limestone water.

The chemical reason why the carbonates render silica harmless is fully explained in the chapter on Colloids. Other hard waters have a permanent hardness caused by the presence of chlorids of calcium and sulfates of calcium only make a pellagrous water worse, as they furnish hydrochloric and sulfuric acid to increase the acid intoxication. The carbon dioxid liberated from the carbonates by a similar action of the silica is easily eliminated and therefore comparatively harmless.

This drinking of hard water is so simple that it has not met the approval of many of the medical profession who are looking for something difficult in the cause and prevention of pellagra. The simplest things are always the most scientific. Certain types of mind do not see the simple things at hand. The medical mind has not been trained upon the principle that two plus two are four. The prevention and cure of pellagra take the thoughtful investigator back to first principles.

Now if the spring or well from which a supply of domestic drinking water is drawn is in a soft water district, or the water is a "freestone" water, it will be necessary to make it a "hard" or "limestone" water. The best way to do this is to excavate a considerable reservoir for the spring and wall it with limestone laid in a rich Portland cement mortar. Then take a good quality of limestone broken to about two-inch sizes and put it in the bottom of the spring six inches to a foot thick. Do not permit any clay to collect in the spring. Wells should be walled the same way and the bottom covered with a foot of broken limestone. Clay should not be permitted to collect in the bottom or to wash in from the top. The stirring up of a clay bottom in springs or wells contributes to the pellagrogenic character of the water.

If the water supplies to a town or city are soft or freestone water, all reservoirs should be walled with Portland cement concrete made of broken limestone. The bottoms of such reservoirs should be covered with at least a foot of broken limestone. Filter beds should contain a large proportion of limestone sands from crusher screenings. A live caustic alkalinity should be added in the form of lime water or calcium hydrate in the treatment of the raw water. Daily chemical tests by simple and well known titration methods would insure a safe alkalinity at all times.

For persons to whom these simple measures of prevention are impractical, the treatment of drinking water with lime is suggested. Take about a tablespoonful of lime and place in an ordinary bucketfull of water. Stir and mix thoroughly and permit to settle. Pour off the lime water if too strong, and dilute it with more water. The remaining lime in the bucket can be treated with more water. When both buckets of water are pleasant to the taste, they will be so alkaline as to prevent pellagra.

Now all of these foregoing suggestions as to the prevention of pellagra are not so profound as to require submission to the Rockefeller Commission or the Carnegie Foundation. They are scientific rather than profound. Since they are scientific, they are also simple. All scientific facts are simple. The average colored woman in the pellagrous area who scrubs and does washing knows when the water is soft or hard. It is high time the medical profession in the examination of the disease called pellagra, got down from an abstruse discussion of toxins, serums, parasites, unbalanced diet and proteid starvation. Let us study the dirt of the ground, the common clay of pellagrous districts and the water supplies derived therefrom. Since pellagra is a silica intoxication, why quibble over many things while the good people of the South die of the disease. The true object of such a study as this is not impossible academic discussion, but the prevention and cure of pellagra. True fame and credit is due to the physician who prevents and cures this disease, rather than to him who evolves, promulgates and defends the most impossible theory.

CHAPTER XII.

THE TREATMENT OF PELLAGRA.

The rational treatment of pellagra follows the classical lines of the treatment of all mineral intoxications:

1. An antidote to the poison.
2. The elimination of the poison already in the system.
3. Building up the depleted organism.
4. Symptomatic treatment of the manifestations.

1. It is well known that colloidal silica is innocuous in the presence of the alkaline carbonates and the carbonates of the alkaline earths. Therefore the antidote of silica consists in getting into the system such simple remedies as the carbonates of calcium, magnesium and sodium. Since such a small amount of silica is necessary to produce the intoxication, and since the carbonates neutralize such large quantities of silica in proportion to the amount of carbonate used, the carbonates can be administered in very small and attenuated doses.

As there is an excess of hydrochloric acid in the stomach in cases of pellagra, and as the chlorids of calcium and sodium do not antidote silica, it is desirable that medication be administered hypodermically, at least in the early part of the treatment. For hypodermic administration, it is necessary to use a neutral, non-irritant preparation. For this purpose Alessandrini and Scala have suggested trisodic citrate (sodium citrate).

A ten per cent solution of sodium citrate is prepared by dissolving 10 grams of pure neutral sodium citrate in 100 cubic centimeters of distilled water. If there is any sediment, the solution should be filtered.

For administration the solution is drawn up into an ordinary hypodermic syringe. It should be injected in one cubic centimeter doses into the deep tissues of the shoulders, back or gluteal region. At the first, the injections are made once a day. After about two weeks the injections are made on alternate days. Near the end of treatment the interval may be a day or two longer.

Some persons are sensitive to these injections and make considerable objection. In such cases, the remedy can be given by the mouth. This requires that more of the medicine be given. We have secured excellent results by giving 2 c.c. by the mouth three times a day.

Sodium citrate given hypodermically becomes sodium carbonate and neutralizes the silica.

The ordinary case of pellagra will require from one to two months of such antidotal treatment. At the same time and afterward tonics and alteratives should be given to rid the system of the morbific material built up by the chronic intoxication, and to build up the digestion and assimilation.

During the treatment with sodium citrate, sodium carbonate or bicarbonate can be administered by dissolving the powdered salt in water, or by dissolving the tablets in water. The amount of this dosage can readily be regulated by the physician.

During all the time of treatment, the silicious pellagrogenic water should be withdrawn and the patient required to drink copiously of hard or limestone water having a temporary hardness caused by the carbonates of calcium and magnesium. This should be continued after treatment to prevent a recurrence.

2. The bowels must be treated so that there will be no constipation or diarrhoea. In the stage of constipation they must be cleaned out so that there is at least a complete evacua-

tion every day. If there is obstinate constipation at first, it must be relieved by enema. The pellagrous condition does not demand drastic purgatives or the use of any drug that will further exhaust the water of the system. Such vegetable remedies as cascara and podophyllin are suggested.

Excretion by the kidneys must be stimulated. The amount of urine and mineral solids must be brought up to the normal. The same observations apply as to drastic remedies. Triticum repens is indicated to relieve burning and urinary irritation.

Removal of noxious wastes is equally indicated. For this there is no better remedy than echinacea. It can be given in large doses without injury.

3. As tonics to build up the appetite, the digestion and assimilation, arsenicum, alb., nux vomica and compound syrup of hypophosfites are suggested. The skin symptoms would also suggest the arsenic. The cure of cases of pellagra with cacodylate of sodium depends upon the sodium as antidote and the arsenic as tonic.

4. A number of lotions and ointments can be used upon the skin lesions.

Milk of magnesia and calcium lactate can be given for the acid burning in the mouth and stomach. Hiccough can be controlled by the mechanical treatment of the phrenic nerve. Vomiting by calcium lactate or by concussion of the fifth thoracic vertebra.

While pellagra is being successfully treated by the hypodermic administration of a ten per cent solution of sodium citrate, without any other medication, and without change of work, domicile, diet or environment, we believe in the symptomatic treatment of the manifestations in addition to the chemical antidote to the silica poison.

There are many preparations of the various remedies indicated in the symptomatic treatment of pellagra. The pharmacy of these preparations is excellent. From the viewpoint of physicians of different schools of medical practice, they leave nothing to be desired in dependable remedies. A reason-able number of these of different kinds we have attempted to enumerate with their name and dosage according to the school of practice in which they are prescribed.

Pyrosis.

Sodium bicarbonate, 1 to 2 grams.

Dissolve in one-fourth glass of water.

Take twenty minutes after eating.

Milk of magnesia, 15 c.c.

In one glass of water.

Give 3 times a day.

Until patient evidences a desire for acids.

Calcium lactate, 1 tablespoonful in a glass of water twice a day.

Liquor Calcis, 1 tablespoonful in a glass of water twice a day.

Condurango (Astier), one teaspoonful in a glass of water after meals.

In chronic cases with pronounced hyperacidity:

Hydrastis, pulv.

Ginger, pulv.

Colombo, pulv.

Bismuth subnitrate; aa 30 grams.

Magnesium carbonate, 120 grams.

Mix. Give from one half teaspoonful to a teaspoonful in 60 cubic centimeters of water after eating.

Bismuth subnitrate, dose from one-fifth of a gram to one gram.

Bismuth sub-gallate, dose from one-fifth to two-thirds of a gram; three to ten grains.

Also used as an ointment with lanolin, or with equal parts of lanolin and zinc ointment, one dram of the subgallate to the ounce of the mixture.

Cerous oxalate, dose one grain every three hours. Indicated in gastric irritation and vomiting. In the disordered stomach of chronic wasting diseases.

Arsenic, arsenicum alb. Not to exceed one-hundredth of a grain triturated with sugar of milk. Fowler's solution, one-fourth minim to five minims.

Arsenicum alb. The Homeopathic preparation triturated with sugar of milk.

Constipation.

Magnesium sulf., 6 drams, 24 grams.

Echinacea, 4 drams, 15 c.c.

Iris, 1 dram, 4 c.c.

Water q. s., 4 oz., 120 c.c.

Give one dram, 4 c.c. in half a glass of water every three hours.

Cascara Sagrada.

Fluid extract. Tonic, three to ten minims. Laxative, five to twenty-five drops four times a day.

Rheum, Rhubard.

Fluid extract. Dose from a half to two drams.

Specific medicine Rheum. Dose one to twenty minims.

Podophyllum. Fluid extract. Dose five to ten grains.

Podophyllin resin. Dose one-eighth grain.

Specific medicine podophyllum. Dose one-fourth to te minims.

Iris. Fluid extract, dose five to sixty minims.

Specific medicine iris, dose one-fourth to five minims.

For a diarrhoea due especially to mucous colitis:

Magnesium sulfate, 2 drams to 4 ounces of water.

Give one teaspoonful every three hours.

For nervous regurgitation:

Specific medicine eupatorium. Ten to twenty drops every two hours.

For gastric ulceration.

Specific medicine geranium.

Fifteen minims every three hours.

Colorless hydrastis:

Ten minims every three hours.
For retention of urine:
Specific medicine gelsemium.
Large doses of five to ten minims to effect.
Retention due to paralysis:
Give strychnine or nux vomica.
For elimination by the urine:
Potassium acetate:
One to twenty grains in water.
Delusions:
Specific medicine hyoscyamus.
One to ten minims.
Fluid extract of hyoscyamus.
Five to twenty minims.
Melancholia:
Cannabis Indica.
Fluid extract of Cannabis Indica.
One to five minims.
Specific medicine Cannabis.
One to ten minims.
See also:
Cimicifuga, pulsatilla, staphysagria and hellebore.

Reconstructive Tonic.

Tinct. Capsium, 1 dram.
Sp. Med. Xanthoxylum, 5 drams.
Sp. Med. Phytolacca, 2 drams.
Sp. Med. Chionanthus, 3 drams.
Sp. Med. Cinchona, 6 drams.
Water q. s., 4 ounces.

Give 1 dram in one-half glass of water after meals and at bed time. Continued until patient is normal.

Many other remedies, among them emetine, picric acid, the sulfites, and sulfocarbolates, have been used with success in indicated cases. In the symtomatology of pellagra the whole field of materia medica is open to the trained prescriber. Treat the patient, not the pellagra. The patient is the morbid entity.

The crucial test of any method of prevention or treatment is clinical results. No research is complete unless its conclusions can be verified in the endemic or epidemic field and at the bedside. In concluding this work it is a pleasure to be able to state that every conclusion of the research has been submitted to these tests with success.

In Italy the methods suggested by Alessandrini and Scala have been taken up by governmental agencies. They have been applied to the treatment of the water supplies in the pellagrous zones. This is already well known to sanitarians. Their work has been published in Italian and English. The alkaline treatment is meeting with success. Pellagra is being prevented and cured without change of labor, domicile, diet or sanitary environment.

Since the writer first published the account of the Italian research in medical journals in the United States, many physicians have been using the methods suggested. Great numbers of letters have been received from all over the pellagrous area testifying to the efficacy of the alkaline treatment and to the correctness of the statement that pellagra is a chronic acid intoxication limited to the areas where the drinking water is derived from clay soils. Such letters have been received from Texas, Louisiana, Oklahoma, Arkansas, Mississippi, Alabama. Georgia, Tennessee, Kentucky and California. At the last conference of medical officers of the state of Louisiana, it was stated that every physician reporting the use of the alkaline treatment was curing pellagra.

The recent efforts of the United States Public Health Service to becloud the issue and hinder progress in the suppression of pellagra have not met with general success. A series of silly experiments in the State Penitentiary of Mississippi are not worthy of being dignified by notice were it not for the fact that they have back of them in their publicity propaganda the prestige and the frank of the government. The organs of organized medicine have quoted them with approval, but they have been criticised and questioned by progressive journals and by meetings of physicians in the pellagrous area. Such efforts can only retard and hinder but not stop the progress of science. The sacrifice of a few thousand more lives because of the delay will perhaps repay these officials for their attempt to block the way of therapeutic progress.

The criticism of Sandwith (Lancet, London, Oct. 23, 1915,) that Egypt is not a clay country, does not seem to express the mature judgment of this distinguished investigator. It would seem that Sandwith had not apprised himself of the full import of the investigations and determinations of Alessandrini and Scala. The alluvial of lower Egypt is a well leached deposit from the igneous and crystalline rocks of Upper Egypt. Sandy silicious soils with smaller amounts of clay are very pellagrogenic if the water supply be derived from them.

More recently Alessandrini and Scala (Policlinico, Roma, Jan. 16, 1916) have reported the success of their treatment all over Italy. In this paper they state that they have met nothing that contradicts their findings, and that without change of domicile, diet, labor or sanitary environment, pellagrins are being cured by the administration of sodium citrate. In this one paper they report a series of forty-four cases.

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